Clinical Guideline

Familial breast cancer:

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

Draft Guideline

Update of clinical guideline 14 and 41.

This guidance is an update of NICE clinical guideline 14 (published May 2004) and NICE clinical guideline 41 (published July 2006) and will replace them.

New and updated recommendations have been included on the classification and care of people at risk of familial breast cancer and the management of breast cancer and related risks in people with a family history of breast cancer.

Where recommendations are shaded in grey and end **[2004]** the evidence has not been updated since the original guideline. Yellow shading in these recommendations indicates where wording changes have been made for the purposes of clarification only.

You are invited to comment on the new and updated recommendations in this guideline only. These are marked as **[2013]** if the evidence has been reviewed but no change has been made to the recommendation, or **[new 2013]** if the evidence has been reviewed and the recommendation have been added or updated.

Appendix G contains recommendations from the **[2004]** and **[2006**] guideline that NICE proposes deleting in the 2013 update. This is because the evidence has been reviewed and the recommendation has been updated or because NICE has updated other relevant guidance and has replaced the original recommendations. Where there are replacement recommendations, details are provided. Where there is no replacement recommendation, an explanation for the proposed deletion is given. You are invited to comment on the deleted recommendations as part of the consultation on the 2013 update.

The original NICE guideline and supporting documents are available from www.nice.org.uk/guidance/CG41

Contents

Foreword

Breast Cancer is the most commonly diagnosed cancer in the UK and more than 48,000 women and around 300 men are diagnosed with breast cancer each year. Of all people diagnosed with breast cancer, about one in five has a family history of the disease.

Where there is a history in the family of several breast or other cancers, such as ovarian or prostate cancer, this may increase an individual's risk of developing breast cancer, much of this excess risk is at a younger age than is usually expected.

People with a family history of breast cancer face a myriad of complex and sometimes difficult choices such as: testing for particular "faulty" genes; how to use genetic test results; additional surveillance; preventive measures (including sometimes surgery); informing and involving other members of the family who may be affected; and considerations about fertility and family planning.

Use of these guidelines will help healthcare practitioners, in partnership with patients, to better identify who is at risk and how their care and future wellbeing can be optimised to detect breast cancer as early as possible when treatment is likely to be more successful, or ideally, prevent it occurring in the first place. Ensuring that all those who would benefit from enhanced surveillance do so, will be a challenge for a stretched health service but one that must be met if we are to make the most of the opportunities for early detection.

The first versions of these guidelines provided information on the classification and care of women at risk of familial breast cancer. These guidelines provide an update reflecting progress in research and treatment since they were originally published and also include men, because a family history of breast cancer can pass down the male as well as the female line of a family.

In addition, these new guidelines provide information on the care and treatment for people with a family history who also have a personal history of breast cancer, who were not covered by previous guidance. The recommendations in this guideline cover both women and men unless otherwise specified.

Patient organisations continue to report that patients and their families experience wide variations in practice, services and responsiveness to patients' needs. The Guideline Development Group (GDG) has been greatly facilitated in its task by the invaluable contribution of expert patient representatives as well as clinicians, academics and researchers representing the many specialities that this topic involves. All members of the GDG share a collective sense of urgency that these variations in practice are addressed so that all people affected by a family history of breast cancer have timely access to the care and treatment that they need.

Ms Maggie Alexander
Chair

Prof Gareth Evans
Clinical Lead

Key priorities

Family history and carrier probability

- When available in secondary care use a carrier probability calculation method with demonstrated acceptable performance (calibration and discrimination) as well as family history to determine who should be offered referral to tertiary care. Examples of acceptable methods include BOADICEA and the Manchester scoring system. **[new 2013]**

Information and support

- To ensure a patient–professional partnership, patients should be offered individually tailored information, including information about sources of support (including local and national organisations). **[2004]**

Carrier probability at which genetic testing should be offered

- For a person with no personal history of breast cancer, offer genetic testing in tertiary care to a family member with breast or ovarian cancer if their combined *BRCA1* and *BRCA2* mutation carrier probability is 10% or more (or they have a Manchester score of 15 or more). **[new 2013]**

- Offer genetic testing in tertiary care to a person with no personal history of breast or ovarian cancer if their combined *BRCA1* and *BRCA2* mutation carrier probability is 10% or more, when they have a first-degree affected relative with a carrier probability of 20% in the family but is unavailable for testing (or a Manchester score of 17 or more). **[new 2013]**

Surveillance for women with no personal history of breast cancer.

- Offer annual mammographic surveillance to all women:
  - aged 40-49 years at moderate risk of breast cancer.
  - aged 40 years and over at high risk of breast cancer. **[new 2013]**

- Offer annual MRI surveillance to all women:
  - aged 20-49 years with a *TP53* mutation
  - aged 20-49 years with a greater than 30% probability of being a *TP53* carrier
  - aged 30-49 years with a *BRCA1* or *BRCA2* mutation.
  - aged 30-49 years who have not had a genetic test but are at greater than 30% probability of being a *BRCA1* carrier. **[new 2013]**

Surveillance for people with a personal history and a family history of breast cancer.

- Offer annual MRI surveillance to all women aged 30–49 years with a personal history of breast cancer who are at high risk of contralateral breast cancer or have a *BRCA1* or *BRCA2* mutation. **[new 2013]**

- Offer annual mammographic surveillance to all women aged 50–69 years with a personal history of breast cancer who are at high risk of contralateral breast cancer or have a *BRCA1 or BRCA2* mutation. **[new 2013]**

Chemoprevention for women with no personal history of breast cancer

- Offer tamoxifen[1] or raloxifene[2] for 5 years to post-menopausal women at high risk of breast cancer unless they have a past history of thromboembolic disease or endometrial cancer. **[new 2013]**

Risk-reducing mastectomy for women with no personal history of breast cancer.

- All women considering bilateral risk-reducing mastectomy should be able to discuss their breast reconstruction options (immediate and delayed) with a member of a surgical team with specialist oncoplastic or breast reconstructive skills. **[2004]**

[1] At the time of consultation (January 2013), tamoxifen did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[2] At the time of consultation (January 2013), raloxifene did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information

Key research recommendations

- **Further research is recommended into developing and validating models for calculating carrier probability which incorporate additional data, such as the molecular pathology of tumours and the prevalence of mutations in different ethnic groups. [new 2013]**

This guideline recommends offering genetic testing to people with a 10% likelihood of carrying a *BRCA1/2* mutation and considering testing at a 5% likelihood threshold. Models to assess the likelihood of a *BRCA1/2* mutation need to be improved because their estimates still have wide confidence margins. Models are sensitive to population prevalence of mutations and need adjustment for pathological subtypes of breast and ovarian cancer which are particularly associated with *BRCA1* mutations. Improving the predictive powers of these models will provide more cost-effective testing.

- **Research is recommended to determine the benefits and harms of creating rapid access to genetic testing for people with newly diagnosed breast cancer. This research should address the optimum model for service delivery and organisation, the clinical and cost effectiveness of such a change, uptake outcomes and patients' experience. [new 2013]**

There is no clear evidence base for rapid genetic testing at the time of diagnosis of primary breast cancer. Knowledge of genetic status may increase uptake of risk-reducing mastectomy and in future guide first-line chemotherapy treatment. To be useful for such decision-making, results of genetic tests are needed within 4 weeks of diagnosis. This creates logistic problems in providing enough information for considered decision-making and delivering results of genetic tests in a supportive environment. Some GDG members were of the opinion that people had enough to cope with shortly after diagnosis without additional worries about genetic testing. However, others thought that early knowledge of genetic status would help decisions about surgery thus avoiding the need to consider this at a future date. For example, initial treatment by wide local excision often necessitates radiotherapy, which makes an acceptable cosmetic operation more challenging. Genetic counselling to facilitate such decisions soon after diagnosis would require reorganisation of current services.

- **Research is recommended to establish the risk and benefits of MRI surveillance compared with mammography in women over 50 years with a personal history of breast cancer. Studies should include sub-analysis for breast density. [new 2013]**

There have been at least six large trials of MRI surveillance in women at high risk of breast cancer. However, none of these contained enough women to assess the potential benefit of MRI over mammography alone in women over 50 years. After 50 years of age mammography becomes more sensitive and the trade-off between sensitivity and specificity may make MRI less cost effective. Although breast density decreases with age, and particularly after the menopause, there is no sudden change at any particular age. For this reason breast density should be included as a confounding variable.

- **A randomised controlled trial is recommended to compare the clinical and cost effectiveness of aromatase inhibitors and tamoxifen for reducing the incidence of breast cancer in women with a family history of breast or ovarian cancer. [new 2013]**

This guidelines recommends offering raloxifene or tamoxifen to women at high risk of developing breast cancer and considering such treatment as chemoprevention for women at moderate risk. One randomised study in North America has showed an aromatase inhibitor (exemestane) to be effective for the primary prevention of breast cancer. However, there has been no randomised control trial comparing the use of aromatase inhibitors with tamoxifen or raloxifene (selective oestrogen receptor modulators or SERMS). Such a trial could better inform women of the best available approach for chemoprevention of breast cancer.

- **Further research is recommended to compare psychosocial and clinical outcomes in women who chose and women who do not choose to have risk-reducing surgery. [new 2013]**

Many women are happy with their decision to undergo risk-reducing surgery. However some women do subsequently regret this choice. A greater understanding of the factors that predict satisfaction or regret will help to guide women's choices in the future. Studies show that risk-reducing surgery significantly reduces risk of breast cancer, but there is insufficient evidence to decide between, for example, skin sparing mastectomy and total mastectomy. The pros and cons of risk-reducing surgery in women with a diagnosis of cancer also need further study.

Methodology

What is a Clinical Guideline?

Guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances – these can include prevention and self-care through to primary and secondary care and on to more specialised services. NICE clinical guidelines are based on the best available evidence of clinical and cost effectiveness, and are produced to help healthcare professionals and patients make informed choices about appropriate healthcare. While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

When this guideline was commissioned in 2010 (see below), clinical guidelines for the NHS in England, Wales and Northern Ireland were produced in response to a request from the Department of Health (DH). Before deciding whether to refer a particular topic to the National Institute for Health and Clinical Excellence (NICE) they consult with the relevant patient bodies, professional organisations and companies. Once a topic is referred, NICE then commissions one of four National Collaborating Centres (NCCs) to produce a guideline. The Collaborating Centres are independent of government and comprise of partnerships between a variety of academic institutions, health profession bodies and patient groups.

Updating a NICE clinical guideline

The NICE guideline on 'The classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care' (CG14) was developed by the School of Health and Related Research, University of Sheffield. (ScHARR) and published in May 2004. In July 2006 the recommendations in CG14 on 'Magnetic Resonance Imaging (MRI) for breast cancer surveillance' were updated by the National Collaborating Centre for Primary Care (NCC-PC) and the guideline was subsequently re-issued as CG41. Both CG14 and CG41 were developed and updated using the methodology recommended by NICE at that time.

Guidelines developed by NICE are published with the expectation that they will be reviewed and updated as is considered necessary. In October 2010 the National Collaborating Centre for Cancer (NCC-C) was asked by NICE to update CG41 in accordance with the NICE guideline development process outlined in the 2009 edition of the guidelines manual (NICE, 2009). The NCC-C was also asked to produce a short clinical guideline on 'The diagnosis and management of affected women with hereditary breast cancer' which had been referred to NICE by the Department of Health in July 2010.

The criteria for deciding the update status of a clinical guideline is defined in the guidelines manual (NICE, 2009) and requires a search for new evidence, using versions of the original search strategies, and to seek the views of stakeholders, healthcare professionals and patients to identify any change in practice or additional relevant published evidence.

Therefore this guideline updates and replaces both CG14 and CG41 and incorporates a new short clinical guideline on the management of breast cancer in women and men who have a family history of breast cancer. Any sections of CG14 or CG41 that have not been amended are integrated within this updated document.

Changes in NICE guideline development methodology since 2004 and 2006 mean the way information is presented may, at times be inconsistent (for example, the style of review write-up and 2013 recommendations are not graded according to the strength of the evidence unlike those in CG14).

Recommendations are marked **[2004]**, **[2006]**, or **[New 2013**]. This is to indicate the year of the last evidence review.

- **[2004**] indicates that the evidence has not been updated and reviewed since 2004.
- **[2006]** indicates that the evidence has not been updated and reviewed since 2006.
- **[new 2013]** indicates that the evidence has been reviewed and the recommendation have been added or updated.

All supporting text from updated and new topics presented in this guideline have been highlight**e**d and labelled **[new 2013**]. The background text which accompanies recommendations from CG14 and CG41 has been revised to reflect current practice. It should be noted that some recommendations from CG14 and CG41 where the evidence has not been updated have been revised under the current NICE equalities policy, and the term 'women' has been changed to 'people' where appropriate.

For simplicity and clarity the guideline will be referred to by its short title 'Familial breast cancer' throughout the remainder of this document.

Who is the Guideline intended for?

This guideline does not include recommendations covering every detail of the 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. Instead this guideline has tried to focus on those areas of clinical practice (i) that are known to be controversial or uncertain; (ii) where there is identifiable practice variation; (iii) where there is a lack of high quality evidence; or (iv) where NICE guidelines are likely to have most impact. More detail on how this was achieved is presented later in the section on 'Developing Clinical Evidence Based Questions'.

This guideline is relevant to all healthcare professionals who are responsible for the classification and care of women at risk of familial breast cancer and the management of breast cancer and related risks in people with a family history of breast cancer, as well as to the patients themselves and their carers. It is also expected that the guideline will be of value to those involved in clinical governance and commissioning in primary, secondary and tertiary care to help ensure that arrangements are in place to deliver appropriate care for the population covered by this guideline.

The remit of the Guideline

Guideline topics selected by the Department of Health identify the main areas to be covered by the guideline in a specific remit. The following remit for this guideline was received from NICE in October 2010:

- To update the clinical guideline on 'Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care
- To produce a short clinical guideline on the diagnosis and management of affected women with hereditary breast cancer'.

Involvement of Stakeholders

Key to the development of all NICE guidance is the involvement of relevant professional and patient/carer organisations that register as stakeholders. Details of this process can be found on the NICE website or in the 'NICE guidelines manual' (NICE 2009). In brief, their contribution involves commenting on the draft scope, submitting relevant evidence and commenting on the draft version of the guideline during the end consultation period. A full

list of all stakeholder organisations who registered for the guideline on familial breast cancer can be found in Appendix D4.

The Guideline Development Process – Who Develops the Guideline?

Overview

The development of this guideline was based upon methods outlined in the 'NICE guidelines manual' (NICE, 2009). A team of health professionals, lay representatives and technical experts known as the Guideline Development Group (GDG) (Appendix D1), with support from the NCC-C staff, undertook the development of this clinical guideline. The basic steps in the process of developing a guideline are listed and discussed below:

- using the remit, define the scope which sets the inclusion/exclusion criteria of the guideline
- forming the GDG
- developing clinical questions
- identifying the health economic priorities
- developing the review protocol
- systematically searching for the evidence
- critically appraising the evidence
- incorporating health economic evidence
- distilling and synthesising the evidence and writing recommendations
- agreeing the recommendations
- structuring and writing the guideline
- consultation and validation
- updating the guideline.

The Scope

The remit was translated into a scope document by the Guideline Development Group (GDG) Chair and Lead Clinician and staff at the NCC-C in accordance with processes established by NICE (NICE 2009). The purpose of the scope was to:

- set the boundaries of the development work and provide a clear framework to enable work to stay within the priorities agreed by NICE and the NCC-C and the remit set by the DH
- inform professionals and the public about the expected content of the guideline.
- provide an overview of the population and healthcare settings the guideline would include and exclude
- specify the key clinical issues that will be covered by the guideline
- inform the development of the clinical questions and search strategy

At this stage it was agreed with NICE to combine the update of CG14 and CG41 with the new short clinical guideline into one common scope and to rename the guideline the 'Classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer.'

Before the guideline development process started, the draft scope was presented and discussed at a stakeholder workshop. The list of key clinical issues were discussed and revised before the formal consultation process. Further details of the discussion at the stakeholder workshop can be found on the NICE website (www.nice.org.uk).

The scope was subject to a five week stakeholder consultation in accordance with processes established by NICE in the 'NICE guidelines manual' (NICE 2009). The full scope is shown

in Appendix C2. During the consultation period, the scope was posted on the NICE website (www.nice.org.uk). Comments were invited from registered stakeholder organisations, NICE staff and the NICE Guideline Review Panel (GRP)[3]. The NCC-C and NICE reviewed the scope in light of comments received, and the revised scope was reviewed by the GRP, signed off by NICE and posted on the NICE website.

The Guideline Development Group (GDG)

The familial breast cancer GDG was recruited in line with the 'NICE guidelines manual' (NICE 2009). The first step was to appoint a Chair and a Lead Clinician. Advertisements were placed for both posts and candidates were interviewed before being offered the role. The NCC-C Director, GDG Chair and Lead Clinician identified a list of specialties that needed to be represented on the GDG. Details of the adverts were sent to the main stakeholder organisations, cancer networks and patient organisations/charities (Appendix D4). Individual GDG members were selected by the NCC-C Director, GDG Chair and Lead Clinician, based on their application forms. The guideline development process was supported by staff from the NCC-C, who undertook the clinical and health economics literature searches, reviewed and presented the evidence to the GDG, managed the process and contributed to drafting the guideline. At the start of the guideline development process all GDG members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared new, arising conflicts of interest which were always recorded (Appendix D1).

Guideline Development Group meetings

Nine GDG meetings were held between 18th July 2011 and 2nd November 2012. During each GDG meeting (held over either one or two days) clinical questions and clinical and economic evidence were reviewed, assessed and recommendations formulated. At each meeting patient/carer and service-user concerns were routinely discussed as part of a standing agenda item.

NCC-C project managers divided the GDG workload by allocating specific clinical questions, relevant to their area of clinical practice, to small sub-groups of the GDG in order to simplify and speed up the guideline development process. These groups considered the evidence, as reviewed by the researcher, and synthesised it into draft recommendations before presenting it to the GDG. These recommendations were then discussed and agreed by the GDG as a whole. Each clinical question was led by a GDG member with expert knowledge of the clinical area (usually one of the healthcare professionals). The GDG subgroups often helped refine the clinical questions and the clinical definitions of treatments. They also assisted the NCC-C team in drafting the section of the guideline relevant to their specific topic.

Patient/Carer members

Individuals with direct experience of familial breast cancer gave an important user focus to the GDG and the guideline development process. The GDG included three patient/carer members. They contributed as full GDG members to writing the clinical questions, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive

[3] As from 1st January 2012, the Guideline Review Panel (GRP) will be no longer be part of the NICE guideline development process (NICE 2012)

issues and terminology relevant to the guideline and bringing service-user research to the attention of the GDG.

Developing clinical evidence-based questions

Background

Clinical guidelines should be aimed at improving clinical practice and should avoid ending up as 'evidence-based textbooks' or making recommendations on topics where there is already agreed clinical practice. Therefore the list of key clinical issues listed in the scope were developed in areas that were known to be controversial or uncertain, where there was identifiable practice variation, or where NICE guidelines were likely to have most impact.

Method

From each of the key clinical issues identified in the scope the GDG formulated a clinical question. For clinical questions about interventions, the PICO framework was used. This structured approach divides each question into four components: P - the population (the population under study, I -, the interventions (what is being done), C - the comparisons (other main treatment options), O - the outcomes (the measures of how effective the interventions have been). Where appropriate, the clinical questions were refined once the evidence had been searched and, where necessary, sub-questions were generated.

Review of clinical literature

Scoping search

An initial scoping search for published guidelines, systematic reviews, economic evaluations and ongoing research was carried out on the following databases or websites: National Library for Health (NLH) Guidelines Finder (now NHS Evidence), National Guidelines Clearinghouse, Cochrane Database of Systematic Reviews (CDSR), Heath Technology Assessment Database (HTA), NHS Economic Evaluations Database (NHSEED), DH Data, Medline and Embase.

At the beginning of the development phase, initial scoping searches were carried out to identify any relevant guidelines (local, national or international) produced by other groups or institutions.

Developing the review protocol

For each clinical question, the information specialist and researcher (with input from other technical team and GDG members) prepared a review protocol. This protocol explains how the review was to be carried out (Table A) in order to develop a plan of how to review the evidence, limit the introduction of bias and for the purposes of reproducibility. All review protocols can be found in the full evidence review.

Table A Components of the review protocol

Component	Description
Clinical question	The clinical question as agreed by the GDG.
Objectives	Short description; for example 'To estimate the effects and cost effectiveness of…' or 'To estimate the diagnostic accuracy of…'.
Criteria for considering studies for the review	Using the PICO (population, intervention, comparison and outcome) framework. Including the study designs selected.
How the information will be searched	The sources to be searched and any limits that will be applied to the search strategies; for example, publication date, study design, language. (Searches should not necessarily be restricted to RCTs.)
The review strategy	The methods that will be used to review the evidence, outlining exceptions and subgroups. Indicate if meta-analysis will be used.

Searching for the evidence

In order to answer each question the NCC-C information specialist developed a search strategy to identify relevant published evidence for both clinical and cost effectiveness. Key words and terms for the search were agreed in collaboration with the GDG. When required, the health economist searched for supplementary papers to inform detailed health economic work (see section on 'Incorporating Health Economic Evidence').

Search filters, such as those to identify systematic reviews (SRs) and randomised controlled trials (RCTs) were applied to the search strategies when there was a wealth of these types of studies. No language restrictions were applied to the search; however, foreign language papers were not requested or reviewed (unless of particular importance to that question).

The following databases were included in the literature search:

- The Cochrane Library
- Medline and Premedline 1950 onwards
- Excerpta Medica (Embase) 1980 onwards
- Cumulative Index to Nursing and Allied Health Literature (Cinahl) 1982 onwards
- Allied & Complementary Medicine (AMED) 1985 onwards
- British Nursing Index (BNI) 1985 onwards
- Psychinfo 1806 onwards
- Web of Science [specifically Science Citation Index Expanded]
- (SCI-EXPANDED) 1899 onwards and Social Sciences Citation Index (SSCI) 1956 onwards]
- Biomed Central 1997 onwards

From this list the information specialist sifted and removed any irrelevant material based on the title or abstract before passing to the researcher. All the remaining articles were then stored in a Reference Manager electronic library.

Searches were updated and re-run 8–10 weeks before the stakeholder consultation, thereby ensuring that the latest relevant published evidence was included in the database. Any evidence published after this date was not included. For the purposes of updating this guideline, September 2012 should be considered the starting point for searching for new evidence.

Further details of the search strategies, including the methodological filters used, are provided in the evidence review.

Critical appraisal

From the literature search results database, one researcher scanned the titles and abstracts of every article for each question and full publications were ordered for any studies considered relevant or if there was insufficient information from the title and abstract to inform a decision. When the papers were obtained the researcher applied inclusion/exclusion criteria to select appropriate studies, which were then critically appraised. For each question, data on the type of population, intervention, comparator and outcomes (PICO) were extracted and recorded in evidence tables and an accompanying evidence summary prepared for the GDG (see evidence review). All evidence was considered carefully by the GDG for accuracy and completeness.

GRADE (Grading of Recommendations, Assessment, Development and Evaluation)

For interventional questions, studies which matched the inclusion criteria were evaluated and presented using a modification of GRADE (NICE 2009; http://gradeworking group.org/). Where possible this included meta-analysis and synthesis of data into a GRADE 'evidence profile'. The evidence profile shows, for each outcome, an overall assessment of both the quality of the evidence as a whole (low, moderate or high) as well as an estimate of the size of effect. A narrative summary (evidence statement) was also prepared.

Each topic outcome was examined for the quality elements defined in Table B and subsequently graded using the quality levels listed in Table C. The reasons for downgrading or upgrading specific outcomes were explained in footnotes.

Table B Descriptions of quality elements of GRADE

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator or outcomes between the available evidence and the clinical question.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect relative to the minimal important difference.
Publication bias	Publication bias is a systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table C Overall quality of outcome evidence in GRADE

Quality element	Description
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

All procedures were fully compliant with NICE methodology as detailed in the 'NICE guidelines manual' (NICE 2009). In general, no formal contact was made with authors; however, there were ad hoc occasions when this was required in order to clarify specific details.

For non-interventional questions, for example the questions regarding diagnostic test accuracy, a narrative summary of the quality of the evidence was given. The quality of individual diagnostic accuracy studies was assessed using the QUADAS tool (Whiting, *et al.,* 2003).

Needs Assessment

As part of the guideline development process the NCC-C invited a specialist registrar (Appendix D5), with the support of the GDG, to undertake a needs assessment (see also chapter 1 and full needs assessment report). The needs assessment aims to describe current service provision for patients with familial breast cancer in England and Wales, which informed the development of the guideline.

Assessment of the effectiveness of interventions is not included in the needs assessment, and was undertaken separately by researchers in the NCC-C as part of the guideline development process.

The information included in the needs assessment document was presented to the GDG. Most of the information was presented in the early stages of guideline development, and other information was included to meet the evolving information needs of the GDG during the course of guideline development.

Incorporating health economics evidence

The aim of providing economic input into the development of the guideline was to inform the GDG of potential economic issues relating to familial breast cancer. Health economics is about improving the health of the population through the efficient use of resources. In addition to assessing clinical effectiveness, it is important to investigate whether health services are being used in a cost effective manner in order to maximise health gain from available resources.

Prioritising topics for economic analysis

After the clinical questions had been defined, and with the help of the health economics team, the GDG discussed and agreed which of the clinical questions were potential priorities for economic analysis. These economic priorities were chosen on the basis of the following criteria, in broad accordance with the NICE guidelines manual (NICE 2009):

- the overall importance of the recommendation, which may be a function of the number of patients affected and the potential impact on costs and health outcomes per patient
- the current extent of uncertainty over cost effectiveness, and the likelihood that economic analysis will reduce this uncertainty
- the feasibility of building an economic model

For each topic, a review of the economic literature was conducted. Where published economic evaluation studies were identified that addressed the economic issues for a clinical question, these are presented alongside the clinical evidence wherever possible. For those clinical areas reviewed, the information specialists used a similar search strategy as used for the review of clinical evidence but with the inclusion of a health economics filter.

For systematic searches of published economic evidence, the following databases were included:

- Medline
- Embase
- NHS Economic Evaluation Database (NHS EED)
- Health Technology Assessment (HTA)
- Health Economic Evaluations Database (HEED)

Methods for reviewing and appraising economic evidence

The aim of reviewing and appraising the existing economic literature is to identify relevant economic evaluations that compare both costs and health consequences of alternative interventions and that are applicable to NHS practice. Thus studies that only report costs, non-comparative studies or 'cost of illness' studies are generally excluded from the reviews (NICE, 2009).

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE, 2009, Appendix H). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the GDG for a specific topic within the Guideline. There are two parts to the appraisal process; the first step is to assess applicability (i.e. the relevance of the study to the specific guideline topic and the NICE reference case) (Table D).

Table D: Applicability criteria

Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness.
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness.
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration.

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (i.e. the methodological quality, Table E).

Table E: Methodological quality

Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness.
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness.
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration.

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the GRADE table for clinical evidence.

If high-quality published economic evidence relevant to current NHS practice was identified through the search, the existing literature was reviewed and appraised as described above. However, it is often the case that published economic studies may not be directly relevant to the specific clinical question as defined in the guideline or may not be comprehensive or conclusive enough to inform UK practice. In such cases, for priority topics, consideration was given to undertaking a new economic analysis as part of this guideline.

Economic modelling

Once the need for a new economic analysis for high priority topics had been agreed by the GDG, the health economist investigated the feasibility of developing an economic model. In the development of the analysis, the following general principles were adhered to:

- the GDG subgroup was consulted during the construction and interpretation of the analysis
- the analysis was based on the best available clinical evidence from the systematic review
- assumptions were reported fully and transparently
- uncertainty was explored through sensitivity analysis
- costs were calculated from a health services perspective
- outcomes were reported in terms of quality-adjusted life years

Linking to NICE technology appraisals

There are no published technology appraisals (TA) relevant to this guideline.

Agreeing the recommendations

For each clinical question the GDG were presented with a summary of the clinical evidence, and, where appropriate, economic evidence, derived from the studies reviewed and appraised. From this information the GDG were able to derive the guideline recommendations. The link between the evidence and the view of the GDG in making each recommendation is made explicit in the accompanying LETR statement.

LETR (Linking Evidence to Recommendations) statements

As clinical guidelines were previously formatted, there was limited scope for expressing how and why a GDG made a particular recommendation from the evidence of clinical and cost effectiveness. To make this process more transparent to the reader, NICE have introduced an explicit, easily understood and consistent way of expressing the reasons for making each recommendation. This is known as the 'LETR statement' and will usually cover the following key points:

- the relative value placed on the outcomes considered
- the strength of evidence about benefits and harms for the intervention being considered
- the costs and cost-effectiveness of an intervention
- the quality of the evidence (see GRADE)
- the degree of consensus within the GDG
- other considerations – for example equalities issues

Where evidence was weak or lacking the GDG agreed the final recommendations through informal consensus. Shortly before the consultation period, ten key priorities and five key research recommendations were selected by the GDG for implementation and the patient algorithms were agreed. To avoid giving the impression that higher grade recommendations

are of higher priority for implementation, NICE no longer assigns grades to recommendations.

Consultation and validation of the Guideline

The draft of the guideline was prepared by NCC-C staff in partnership with the GDG Chair and Lead Clinician. This was then discussed and agreed with the GDG and subsequently forwarded to NICE for consultation with stakeholders.

Registered stakeholders (Appendix D4) had one opportunity to comment on the draft guideline which was posted on the NICE website between 15 January 2013 and 25 February 2013 in line with NICE methodology (NICE 2012).

The pre-publication process

An embargoed pre-publication of the guideline was released to registered stakeholders to allow them to see how their comments have contributed to the development of the guideline and to give them time to prepare for publication (NICE 2012).

The final document was then submitted to NICE for publication on their website. The other versions of the guideline (see below) were also discussed and approved by the GDG and published at the same time.

Other versions of the Guideline

This full version of the guideline is available to download free of charge from the NICE website (www.nice.org.uk) and the NCC-C website (www.wales.nhs.uk/nccc).

NICE also produces three other versions of the familial breast cancer guideline which are available from the NICE website:

- the NICE guideline, which is a shorter version of this guideline, containing the key priorities, key research recommendations and all other recommendations
- NICE Pathways, which is an online tool for health and social care professionals that brings together all related NICE guidance and associated products in a set of interactive topic-based diagrams.
- 'Information for the Public (IFP'), which summarises the recommendations in the guideline in everyday language for patients, their family and carers, and the wider public

Updating the Guideline

Literature searches were repeated for all of the clinical questions at the end of the GDG development process, allowing any relevant papers published before September 2012 to be considered. Future guideline updates will consider evidence published after this cut-off date.

A formal review of the need to update a guideline is usually undertaken by NICE after its publication. NICE will conduct a review to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

Funding

The National Collaborating Centre for Cancer was commissioned by NICE to develop this guideline. All health economic analyses for this guideline, including the development of

economic models, was performed by Swansea University and funded by the National Collaborating Centre for Cancer.

Disclaimer

The GDG assumes that healthcare professionals will use clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply these guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient and clinical expertise.

The NCC-C disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

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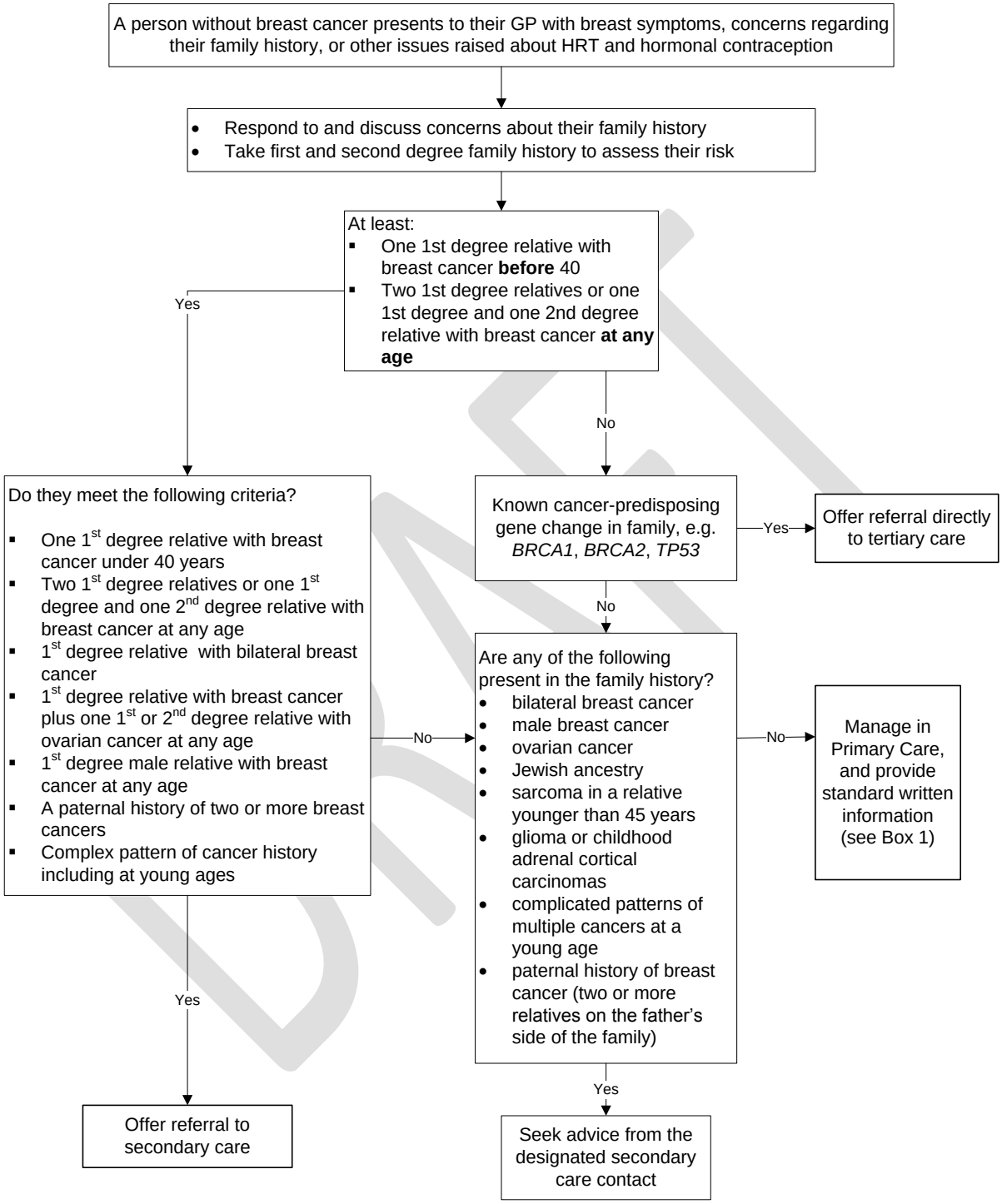
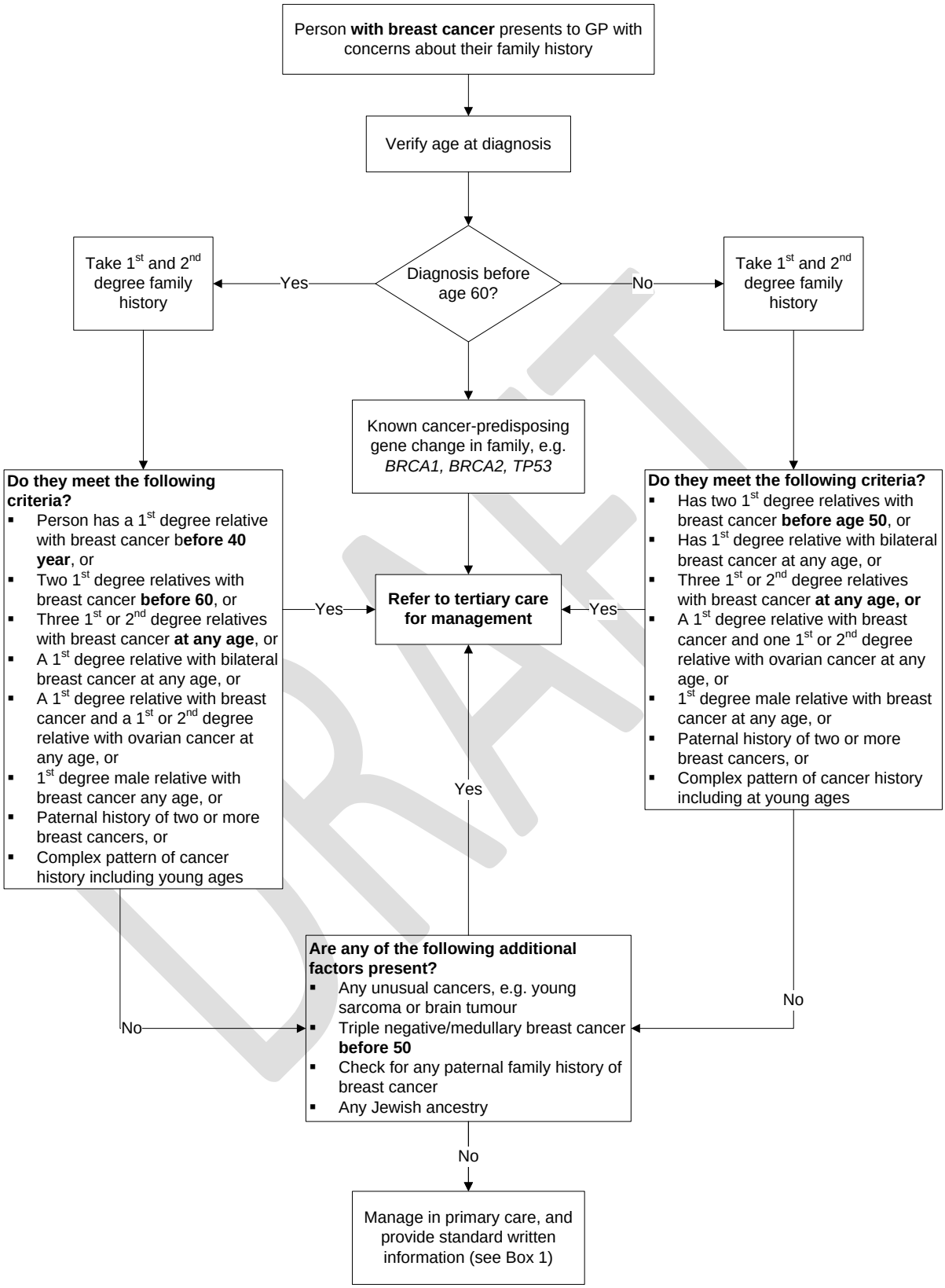
Algorithms

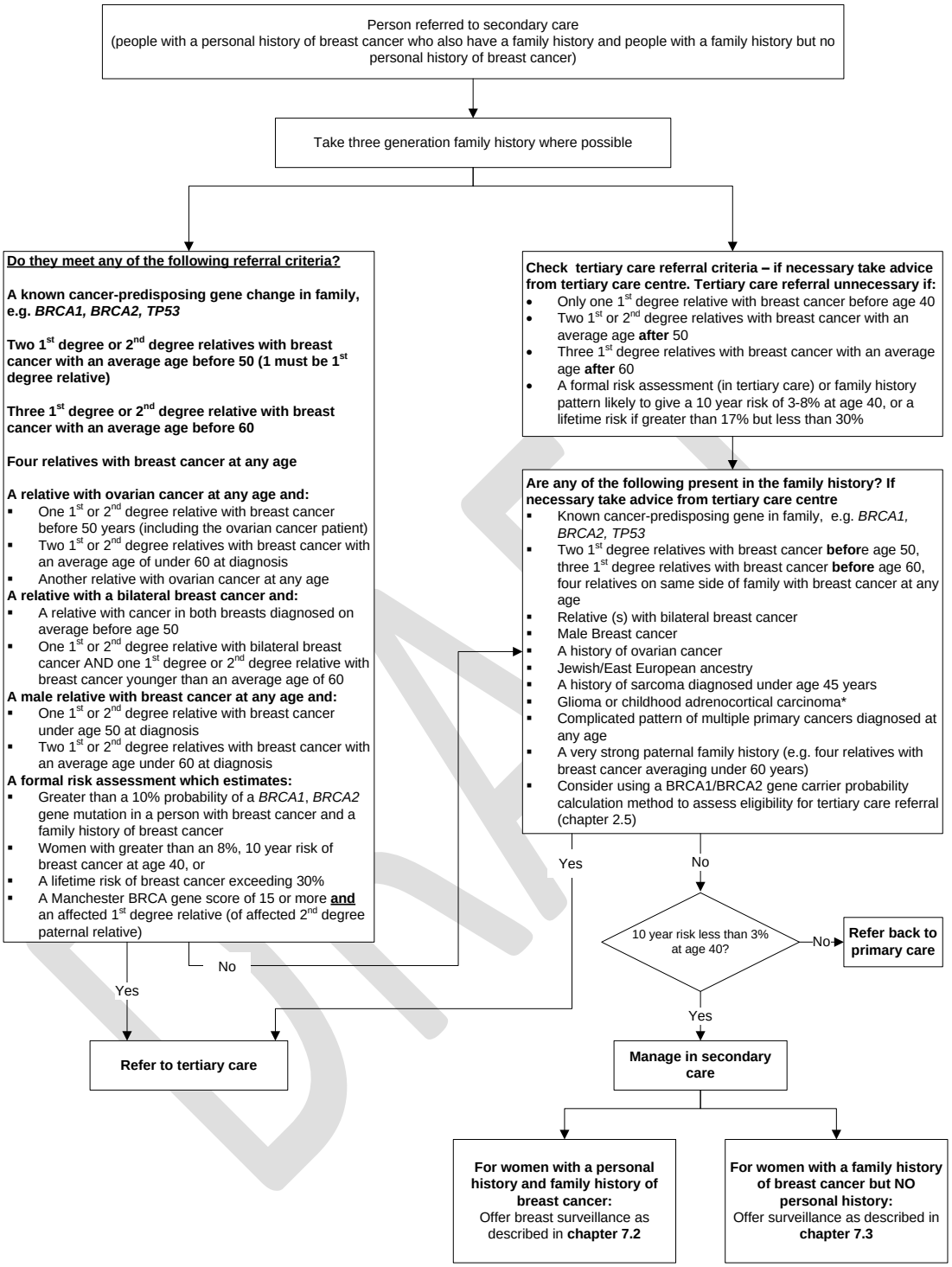
Care and management of people in primary care without a personal history of breast cancer.



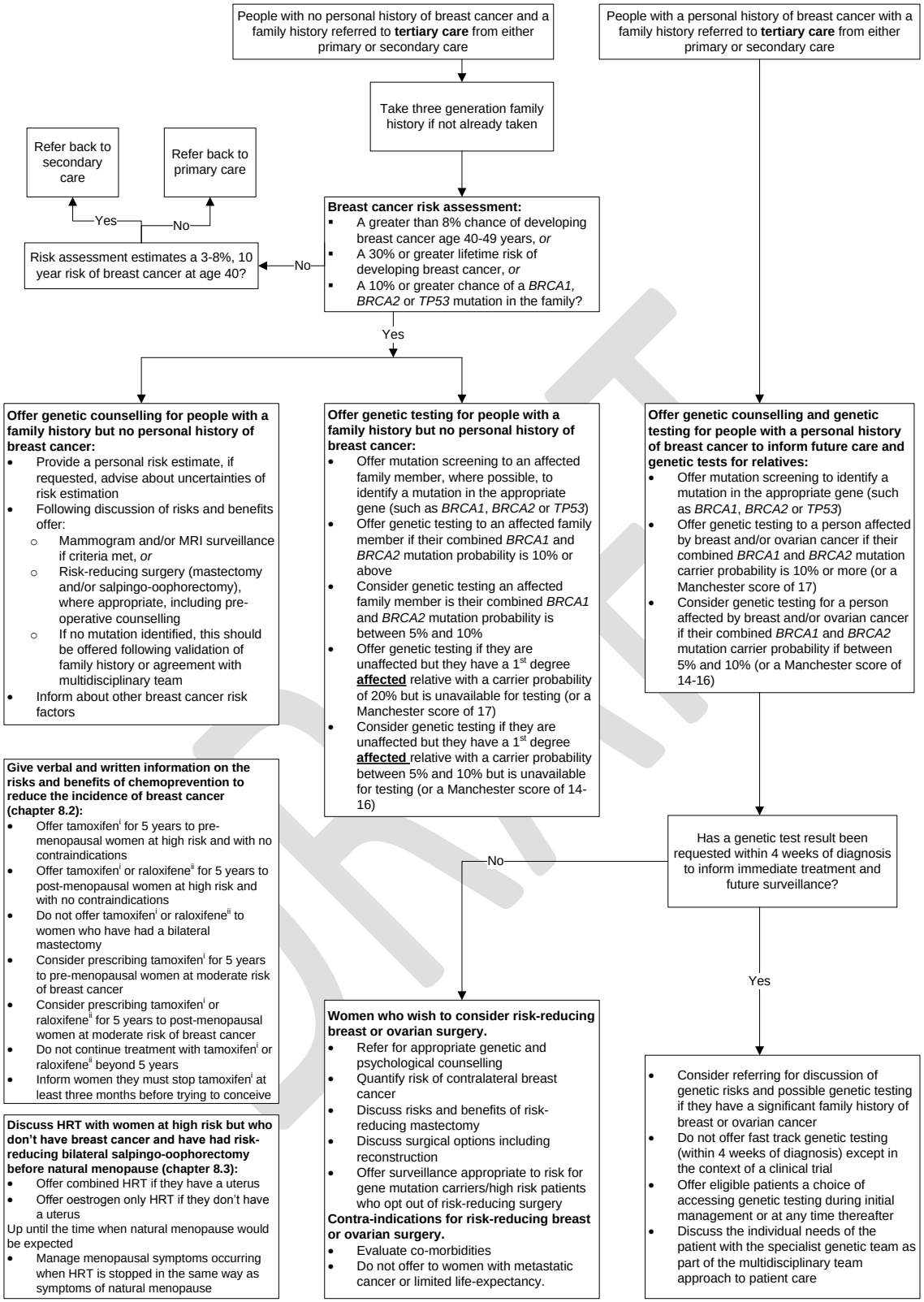
Care and management of people in primary care with a personal history of breast cancer.



Care and management of people in secondary care.



Care and management of people in tertiary care.



[i]At the time of publication (June 2013), tamoxifen did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[ii]At the time of publication (June 2013), raloxifene did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information

1 Epidemiology

1.1 Introduction

Breast cancer is by far the most common cancer diagnosed in women worldwide, with an estimated 1.38 million new female breast cancer cases diagnosed in 2008 (around 23% of all the cancers in women only, and around 11% of all the cancers in men and women together) (Ferlay, *et al.,* 2010). Breast cancer incidence rates are highest in Western Europe and North America, and the incidence of female breast cancer in the UK is estimated to be the 6th highest in Europe. In 2010, there were 49,961 new cases of breast cancer in the UK - 49,564 (99%) in women and 397 (less than 1%) in men. Female breast cancer incidence is strongly related to age, with the highest incidence rates overall being in older women. In the UK between 2008 and 2010, an average of 45% of cases were diagnosed in women aged 65 years and over, and 80% were diagnosed in the 50s and over (Office for National Statistics, 2012). The lifetime risk of developing breast cancer in the UK is estimated to be 1 in 8-10 for women and around 300,000 women are currently alive having been diagnosed with breast cancer in the past 10 years (National Cancer Intelligence Network 2010).

Breast cancer is a multifactorial disease, which may involve an interaction between environmental, lifestyle, hormonal and genetic factors. A family history of breast cancer is associated with an increased risk of the disease with the risk increasing with the number of relatives affected and with the age at diagnosis of the relative – the younger the age of diagnosis the greater the risk (Collaborative Group on Hormonal Factors in Breast Cancer 2001). Based on UK incidence data the probability of a woman aged 20 developing breast cancer by the age of 80 who has no affected relatives is 7.8%; with 1 affected relative, 13.3% and with 2 affected relatives, 21.1%. Also, the younger the relative was when she developed the disease, the greater the risk of developing breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 2001). However, in the majority of affected women, the cause is unknown, rather than due to known high risk genetic or shared lifestyle factors.

The majority of cases of breast cancer arise in women with no apparent close 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). Given that breast cancer is common, a family history of breast cancer does not inevitably point to a shared cause. Hereditary breast cancer is characterized by an unusually high number of family members affected with breast or related cancers, typically at a younger age than observed in the general population. If there have been more cases of breast cancers in families than would be expected by chance alone, it may be that genes transmitted between generations are sufficient to cause or, more likely, contribute to the development of breast cancer.

About 5% of all breast cancers are largely attributable to inherited mutations in specific genes including *BRCA1, BRCA2 and TP53.* The lifetime risk of breast cancer in women with a mutation in one of these genes is substantially increased compared to the general population (Antoniou, *et al.,* 2003). Such an inherited predisposition to breast cancer is usually characterized by early age of onset, a high incidence of bilateral disease and with a family history of other malignancies.

Breast cancer occurring in a woman with a family history of the disease is known as “familial breast cancer”. Sometimes the term “hereditary” breast cancer is used to describe breast cancer in families with an apparently dominant inheritance suggesting that a high penetrance breast cancer risk gene is segregating in that family. However, not all such familial clusters can be explained by known breast cancer susceptibility genes. Breast cancer occurring in a

woman without a family history is often referred to as “sporadic”, but this should not be interpreted as non-genetic, as all breast cancer has a polygenic component to its etiology. Furthermore, some cases of “sporadic” breast cancer occur in women who carry a high-penetrance breast cancer susceptibility gene mutation but do not have a family history of breast cancer.

This NICE guideline provides recommendations for the classification and care of women who are at an increased risk of developing breast cancer because of a family history or they have a high chance of carrying a high-penetrance breast cancer susceptibility allele. The purpose of the needs assessment is to provide a context to the guideline, by providing an overview on the burden of the disease and the current practices in managing individuals affected and at risk of familial breast cancer. A detailed report on the needs assessment is available as a supplement to the guideline.

1.2 Methodology

Routine data from England and Wales pertaining to familial breast cancer was actively sought to inform about the extent of the disease and the current practices at different levels of the health care system in UK. Information from published data and ongoing projects informing the burden of familial breast cancer and ongoing management of patients and families with the disease amongst professionals in the primary, secondary, specialist and laboratory settings were identified.

The process of needs assessment revealed a lack of published data from cancer geneticists and gynaecological oncologists, who play a vital role in the management of patients and families with familial breast cancer. Hence dedicated surveys were carried out in these groups of professionals to build the necessary dataset.

The questionnaire for the cancer geneticists was aimed at obtaining data on the burden of familial breast cancer and current management practice pertaining to referrals, triaging process, risk assessment, genetic testing, screening and advice on risk-reducing surgeries in this group of patients. This group of professionals were also asked to comment on any issues concerning provision of genetic services for familial breast cancer based on individual experience.

The questionnaire for gynaecological oncologists was designed to gather information on the demand familial breast cancer posed on gynaecological services and the practices surrounding risk-reducing surgery, ovarian screening and hormone replacement therapy.

The questionnaires were generated with input from members of the guideline development group (GDG) and then set up as a web based survey by the NCC-C.

The respective web-based surveys were circulated by electronic mail with a cover letter to all the consultant cancer geneticist members of cancer genetics group (CGG) and the consultant gynaecological oncologist members of the British Gynaecological Cancer Society (BGCS).

1.3 Disease Burden

InCRisC (Harris, *et al.,* 2011) was a questionnaire-based multicentre European research project on cancer risk communication, predictive testing and management of familial breast cancer in primary care and by breast surgeons in the United Kingdom, France, Germany and

Netherlands. A total of 197 general practitioners (GP) and 156 breast surgeons from United Kingdom participated in the study.

Just over 44% of the GP's in the InCRisC study reported a consultation involving a family history of breast cancer at least once a month and less than a quarter of them engaged in such consultation at least once a week. Over three quarters of the breast surgeons reported that concerns about family history of breast cancer were raised at least once a week during consultation.

Cancer Geneticist GDG survey data

A total of 27 cancer geneticists representing 17 major genetic centres in England, Wales and Northern Ireland responded to the GDG survey.

16 of the 27 (59.2%) cancer geneticists were referred between 50-150 patients with a family history of breast cancer each month and majority of cancer genetics teams reviewed between 50-150 breast cancer families each month.

Gynaecological Oncologist GDG survey data

Forty one UK consultant gynaecological oncologists responded to the GDG survey. 70% of these gynaecological oncologists were based in hospitals linked to clinical genetics services.

35 of the 41 (89.7%) of the respondents reviewed less than 100 patients with family history of *BRCA* related cancers (breast, ovarian or related cancers) per year and a majority of them reviewed less than 25 patients with *BRCA* related cancers in this period. Most of the gynaecological oncologists performed between 1 and 50 risk-reducing oophorectomies in women with a strong family history of *BRCA* related cancers over a one-year period.

Clinical Molecular Genetics Society (CMGS) audit

The Clinical Molecular Genetics Society (CMGS) produce an annual report of their audit of genetic testing activity undertaken by member laboratories (which comprise nearly all of the UK Regional Molecular Genetic Services and some specialist services)

The 2010-2011 CMGS audit showed that *BRCA* testing accounted for 6.5% of their total annual testing activity. The number of *BRCA* tests have increased over the last decade with a peak during 2007-2008 and have now plateaud off. This peak can be explained by a backlog of testing following publication of CG14 in 2004, which recommended more detailed testing of *BRCA1*/2 than previously done.

The 2010-2011 figures showed a 70% and 74% compliance to target reporting times for routine complex (a full *BRCA1* and *BRCA2* gene screening within an 8 week target) and routine simplex (screening for specific familial *BRCA* gene mutation within a 2 week target) *BRCA* tests respectively. The reporting times measured the interval between the activation of the genetic test to when the results are reported, and because time between taking the sample and activation was not measured, the data does not always accurately reflect the waiting time for patients.

Ethnic minority data

A pilot programme carried out as part of "Ethnic Monitoring in Clinical Genetics", a project by Genetics Interest Group (GIG) in 2003 showed that minority ethnic groups are significantly underrepresented in cancer referrals to clinical genetics services in the UK. Less than 6% of all cancer referrals to clinical genetics services during the pilot period were for members of minority ethnic communities. The pilots were carried out in areas where minority ethnic groups made up approximately 10% of the population.

Data from the “Tipping Points” project undertaken by Leicester cancer genetics services and Genetic Alliance UK suggests that individuals with significant family history of cancers from black and minority ethnic groups (BME) are more likely to be referred later to cancer genetics services in comparison to non-BME group. There was a marked difference in the reasons triggering referrals to cancer genetics services between the two groups. BME groups were more likely to be referred due to a recent diagnosis of cancer or death of a family member. Also of note was that non-BME groups were 9 times more likely to ask for referral because of screening advice compared to BME groups.

“Access to assessment of Familial Cancer Risk by people from minority ethnic backgrounds” is an ongoing Genetics Alliance UK project aiming to explore the reasons for under-representation of individuals from minority ethnic groups with a significant family history of cancer in clinical genetics services, to inform future intervention and service development. Preliminary results from this study has highlighted some important points that could contribute to under-representation of individuals from ethnic minority groups with, or at-risk of familial cancers to genetics services, such as language barrier, difficulties in providing accurate information pertaining to family history, inconsistencies in following guidelines for referrals and cultural influences on peoples attitude and expectations. The study group has made recommendations for service and intervention development based on their findings which includes, a drive towards raising awareness in the minority ethnic communities, routine systematic enquiries about family history of cancers in primary care, availability of simplified referral guidelines and targeted education amongst clinicians involved in the care of patients with family history of cancers.

All the above projects have looked at familial cancers in general rather than familial breast cancer in particular. However, individuals at risk of familial breast cancer form a significant part of these projects.

1.4 Current practice on management of families with familial breast cancer

Referral to local genetic services

A majority of the GP’s and breast surgeons on the InCRisC study agreed that they would refer an unaffected woman with a known family history of *BRCA* mutation for further genetic counselling.

Most genetics centres in the UK have guidelines to direct primary/ secondary health care professionals on how and when to refer individuals with a family history of breast, ovarian or related cancers to cancer genetics services.

Risk assessment and triaging process

About three quarters of the GP’s on the InCRisC study replied that in practice they would not provide information by themselves on lifetime risk of developing breast cancer or the risk of

inheriting a familial *BRCA* mutation, to an unaffected woman with a family history of breast cancers. Most of the breast surgeons agreed that the GP should perform the initial risk assessment in a healthy unaffected woman concerned about her family history of breast cancer. The InCRisC study showed that there are strong views against the current purely reactive (not actively seeking women with a family history of breast cancer) approach to familial breast cancer amongst GP's and surgeons (Harris, *et al.,* 2011).

In a majority of genetic centres, cancer geneticists or genetic counsellors triage patients referred with a family history of breast cancer. Other members of the team involved in triaging include specialist registrars and cancer triage nurses.

Genetic centres use various familial breast risk assessment tools to assess mutation detection probabilities including Manchester scoring system, computerized programmes and manual methods of risk assessment. The Manchester scoring system was the most frequently used tool followed by BOADICEA.

Threshold for genetic testing

The previous familial breast cancer NICE guidance (CG14) recommends genetic testing in affected women with a 20% or greater chance of carrying a mutation in a breast cancer predisposing gene, based on their family history.

In practice, genetic testing is frequently offered to affected women with less than 20% probability of carrying a *BRCA* gene mutation. The GDG survey showed that 42% of cancer geneticists offered genetic testing to an affected woman with a probability of 20% or greater of carrying a *BRCA* mutation. 46% of the cancer geneticists used a lower threshold of 10% or greater to offer genetic testing in an affected woman. Some genetic centres offer genetic testing in affected individuals where the Manchester score is 15 or above. In certain situations, such as young onset "triple negative" breast cancers (estrogen receptor, progesterone receptor and HER2 negative), young onset breast cancer in a small family, or unknown family history, testing is often offered at a lower risk value. In certain populations, such as those of Ashkenazi Jewish, Polish or Icelandic descent, testing for the founder mutations is often offered before full screening of the genes.

Over 65% of the cancer geneticists had offered BRCA1/2 gene mutation testing to unaffected individuals who had a family history of breast, ovarian or related cancers when a test could not first be done in an affected relative. These situations were relatively rare with each geneticist citing no more than 25 such examples per year to date. Testing in such cases was offered when the carrier probability of a *BRCA* mutation was either greater than 20% or 30%.

Surveillance

65% of the cancer geneticists reported that women eligible for annual MRI under NICE CG41 recommendations received it. However, regional variation in availability of MRI surveillance for eligible high-risk women was highlighted in the GDG survey, in some cases between regions covered by one genetic service. Variability was largely attributed to lack of local resources.

A majority of the gynaecological oncologists had offered ovarian screening (usually annual transvaginal ultrasound and CA125 levels) as part of UK Familial Ovarian Cancer Screening Study (UK FOCSS) for unaffected women with a high-risk family history of *BRCA* related cancers, who had not undergone risk-reducing oophorectomy, up until 2010 when the

recruitment for the study ceased. About half of the gynaecological oncologists on the survey have continued offering ovarian screening outside the UK FOCSS.

Risk–reducing surgeries

Approximately 1 in 3 GP's participating in the IncRisC study thought that risk-reducing mastectomy was 'certainly' an option for an unaffected *BRCA* carrier woman, while a small proportion of them (8.7%) did not consider it an option.

The breast surgeons in general considered risk-reducing mastectomy and risk-reducing oophorectomy before the age of 40 as a management option for an unaffected *BRCA* carrier woman. A proportion (6% 'certainly' and 38% 'probably') of the breast surgeons would consider discussing the option of risk-reducing mastectomy with an unaffected woman with a significant family history of young onset breast cancers in the absence of a *BRCA* gene mutation detected in the family. (InCRisC study).

A majority of the gynaecological oncologists (24 of the 36 respondents) would discuss the option of risk-reducing oophorectomy in an unaffected woman with a high-risk family history of breast cancers, with no *BRCA* mutations detected in the family on testing and more so (31 of the 37 respondents) in an affected woman with a past history of breast cancer in the same situation. A vast majority of the participants agreed that they would discuss the option of risk-reducing oophorectomy in unaffected women at 50% risk of familial *BRCA* mutation or known to carry a familial *BRCA* mutation (Gynaecological Oncologist needs GDG survey).

A majority (73.1%) of cancer geneticists would discuss risk-reducing mastectomy in unaffected women with high-risk family history of breast cancers, in the absence of a *BRCA* mutation on testing in the family, while a greater proportion (80.8%) of cancer geneticists would discuss this option if a woman in the same situation was previously affected with breast cancer. All cancer geneticists agreed that they would discuss the option of risk-reducing surgeries in an unaffected woman with a familial *BRCA* mutation.

In contrast to the gynaecological oncologists, a smaller proportion (15.4% and 23.1% respectively) of cancer geneticists would consider discussing risk-reducing oophorectomy with unaffected women or women previously diagnosed with breast cancer with a strong family history of breast cancers, who had no known familial *BRCA* mutation.

Hormonal therapy

All the gynaecological oncologists participating in the GDG survey agreed that they would advise hormone replacement therapy (HRT) in unaffected women, who were at high-risk, following a risk-reducing oophorectomy before the age of 50 years. The risks and benefits of HRT would be discussed. Factors that would influence advice given include previous history of breast cancer, menopausal symptoms and the age of the patient. The choice of HRT would depend on whether the woman still has her uterus. A combined oestrogen and progesterone treatment is being offered for those women who still have their uterus, while oestrogen only replacement is offered for those without. HRT is usually continued till the age of 50, but other factors such as risk of breast cancer, patient's decision and menopausal symptoms might modify this. Gynaecological oncologists would consider HRT as a contraindication in women with a previous diagnosis of oestrogen receptor and progesterone receptor (ER/PR) positive breast cancer, current diagnosis of any type of breast cancer, or if there is a history of liver disease, deep vein thrombosis and pulmonary embolism. Breast oncologists would be involved in discussions while considering HRT in women with previous diagnosis of breast cancer.

88.5% cancer geneticists on the survey agreed that they would discuss the option of HRT, and if necessary refer unaffected high-risk women for advice on HRT following risk-reducing oophorectomy.

Life style advice

IncRisC data suggests that GP's sometimes offered advice on impact of lifestyle on risk of breast cancers in unaffected women with family history of breast cancers. Advice on the impact of alcohol consumption, obesity, oral contraception, exercise, child bearing at younger age and breast-feeding were sometimes but not routinely given to unaffected women with a family history of breast cancer. The breast surgeons followed a similar trend in their advice.

During consultation most cancer geneticists routinely discuss the importance of breast self-examination and regular surveillance for unaffected women with a high-risk family history of breast cancer.

1.5 Comments on genetic service provision

In the GDG survey cancer geneticists raised some important issues for them about the provision of genetics services for patients and families with familial breast cancer. Frequently mentioned issues included considering lower thresholds to offer *BRCA* genetic testing, considering testing in unaffected individuals in the absence of a surviving affected relative, widening the gene testing profile to include other breast cancer predisposing genes and inconsistencies in screening in high-risk groups due to funding issues.

1.6 Summary

The process of needs assessment has highlighted the dearth of routine data informing the burden of the disease and current practice in primary, secondary and specialist care settings in management of individuals at high-risk of familial breast cancers.

The InCRisC study and the GDG surveys have highlighted some important points pertaining to existing practice in management of women at risk of familial breast cancer.

It is not uncommon for cancer geneticists to offer genetic testing in affected individuals with mutation probability lower than the NICE guidance (CG14) recommendation of 20%. Comments from cancer geneticists suggest a move towards increased genetic testing in clinical practice by considering testing at lower threshold (lower than the 20% recommended threshold) and more frequent testing in unaffected individuals than in the past.

Just over 65% of the cancer geneticists said that women with high-risk family history eligible for MRI screening received recommended surveillance. Regional variations in the availability of MRI surveillance for high-risk eligible women are not infrequent. The stated reasons for these variations include problems with funding and lack of resources.

Unaffected women with a family history of breast cancer presenting in a primary and secondary care setting may not always receive advice on the impact of lifestyle factors on breast cancer risks.

A complete report of this needs assessment is available as a supplement to the guideline.

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2 The clinical significance of a family history of breast cancer

The objective of this chapter is to define how to assess and communicate breast cancer risk and the probability that family history is due to a faulty high risk breast cancer gene. This includes:

- classification of different types of risk
- the influence of family history on breast cancer risk,
- cancer risk associated with the family history,
- the influence of family history on carrier probability
- communicating cancer risk and carrier probability

2.1 Clinical classification

The clinical management of an individual with a family history of breast and/or ovarian cancer is determined by two key parameters that each depends on the nature and extent of that family history. These parameters are:

- **Breast cancer risk** - The risk that the individual will develop breast (or ovarian) cancer in the future. Breast cancer risk is frequently expressed as either the lifetime risk of developing the disease or as risk in the next 10 years.

- **Carrier probability** - The probability that the individual carries a deleterious mutation in one of the known breast (or ovarian) cancer susceptibility genes. [A deleterious mutation is one that is known to be associated with a very high risk of developing breast cancer].

These two terms will be used throughout the rest of this guideline.

These parameters are related to each other, as the more extensive the family history the greater the breast cancer risk and the higher the carrier probability. However, it is important that they are clearly differentiated as they influence different management decisions in different ways.

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 cancer risk level, e.g. near population, moderate or high, or categories of carrier probability.

However, it is also recognised that descriptions of people at high and moderate cancer risk will also be necessary in some situations, and that the terms will be used by many people in the clinical setting. As has been made clear in the relevant sections it is not expected that precise cancer risks or carrier probabilities will be calculated in primary or secondary care, but that health care professionals will utilise the algorithms provided (see page 22).

2.2 Breast cancer risk and a family history of breast cancer

The risk of breast cancer in a person with a family history depends on the nature of the family history and on the presence of other risk factors for breast cancer. The cancer risks associated with a family history are modified by other known breast cancer risk factors, including age at menopause, parity, oral contraception, hormone replacement therapy (HRT)

and breast feeding. It is less clear whether and how such factors also modify the risks in *BRCA1* or *BRCA2* carriers.

A person who is a carrier of a deleterious variant in one of the known susceptibility genes is at high risk of developing breast cancer and other cancers. Similarly a person of unknown carrier status with a close family history and characteristics that are associated with a high carrier probability will be at high cancer risk.

Measures/metrics of cancer risk

There are two main types of cancer risk: relative risk and absolute risk. Relative risks are generally reported in observational epidemiology studies but have limited clinical utility and are poorly understood by people seeking advice. Absolute risks are generally of greater clinical relevance than relative risks and can be presented in several ways - various measures of absolute risk are used in this guideline to determine clinical management.

Determining the cancer risk for an individual

Converting published relative risks into absolute risks is computationally straightforward, although not something that is likely to be carried out in secondary or tertiary care. However, it is difficult to estimate cancer risks while taking into account more complex family structures and an increasing level of information such as the number and attained age of unaffected women and their relation to the unaffected person. The Claus tables were generated to provide cumulative cancer risk estimates across a wide range of typical family histories and have been widely used in cancer genetic clinics. However, these were based on a genetic model derived from a single case-control study and population incidence data for North America in the 1980s. In addition, the Claus tables do not account for unaffected relatives. They are unlikely to be accurate for a UK population in the 21st century.

Statistical models such as BRCAPRO, IBIS and BOADICEA models have been developed as computer programmes that can analyse full pedigree data and compute risks for most types of family history. In the case of BRCAPRO and BOADICEA, estimates of *BRCA1* and *BRCA2* carrier probabilities can also be generated. None of the models have been extensively validated for the absolute cancer risk estimates. However, the relative risk estimates used by BOADICEA to generate absolute risks, are very close to the age specific familial relative risks estimated empirically by the Collaborative Group on Hormonal Factors in Breast Cancer (2001).

The determinants for reaching each level of risk category are included and defined in the recommendations within chapter 5, section 5.1.

Table 2.1 summarises the categories and the related care settings for those being assessed for breast cancer risk and carrier probability.

Table 2.1: Summary of categories and related care settings

Breast cancer risk category	10 year breast cancer risk aged 40	Lifetime breast cancer risk from aged 20	Likelihood of a mutation in *BRCA1*/2 or TP 53	Care Setting
Near population risk	less than 3% between age 40 and 50 years (equivalent to less than 1 in 33)	lifetime risk of less than 17% (equivalent to less than 1 in 6)	Very low	Primary care
Moderate risk	a risk of 3–8% between age 40 and 50 years (equivalent to between 1 in 12 to 1 in 33)	lifetime risk of 17% or a greater but less than 30% (equivalent to greater than 1 in 4)	Less than 10%	Secondary care
High risk	a risk of greater than 8% between age 40 and 50 years (equivalent to more than 1 in 12)	a lifetime risk of 30% or greater (equivalent to greater or equal to 1 in 3)	a 10% or greater chance of a faulty *BRCA1*, *BRCA2* or *TP53* gene in the family (equivalent to greater than or equal to 1 in 10)	Tertiary care

Care settings

People who are at near population risk of breast cancer are generally managed in the primary care setting as they are considered not to be at sufficient risk to justify extra surveillance or other interventions to reduce their breast cancer risk. (see also chapter 4)

People who are at moderate risk of breast cancer are generally managed in the secondary care setting as they are considered to be eligible for enhanced surveillance, particularly between the ages of 40 and 49, but do not reach the level of breast cancer risk and/or carrier probability to justify referral to tertiary care. (see also chapter 5)

People who are at high risk of breast cancer and/or a sufficiently high carrier probability are generally managed in the tertiary care setting (see also chapter 5) where they have the possibility of access to enhanced surveillance with MRI, risk-reducing surgery, chemoprevention options and genetic testing. (see also chapter 6)

2.3 Family history-taking

Drawing a family tree is the first step in evaluating the importance of a family history of breast (and other) cancer. This will mean asking the person seeking advice to provide information about all their close blood relatives. The key pieces of information needed are: the age that they have lived to (or died at), what tumours they have had and their age at diagnosis.

Using this information a family tree can be drawn showing the person and their:

- first-degree relatives (mother, father, siblings, children);
- second-degree relatives (grandparents, aunts, uncles, nieces, nephews, half siblings)
- third-degree relatives (great grandparents, great aunts and uncles, first cousins) for a thorough history.

The important features in a family history are:

- young age at onset
- presence of bilateral disease
- multiple cases in the family (particularly on one side)
- other related early onset tumours such as ovary, pancreas, prostate, sarcoma and adrenal carcinoma
- number of unaffected individuals (large families are more informative).

2.4 Accuracy of family history

The reporting of breast cancer in first-degree relatives is nearly always correct. However, the reporting of other malignancies, particularly those in the abdomen and pelvis is less accurate. Similarly, the reporting accuracy reduces for more distant relatives. Cancer diagnoses can be verified from pathology records or death certificates. Family history and verification is an essential part of assessment in a cancer genetics clinic.

Clinical Evidence (2004) (see also full evidence review)

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).

Evidence statements (2004)

Reporting of breast cancer family histories, by women with and without breast cancer, is generally valid. (III)

Completing a family history questionnaire relating to inherited illnesses caused short-term distress, although this did not persist. (Ib)

Poor communication amongst families can impede the collection of family history information. (III)

Postal questionnaires and family history assessment tools are useful instruments to support the identification of women at increased risk of breast cancer. (III)

GPs have been found to prefer computerised programs to collect family history information compared to pen-and-paper methods. (III)

Computer support programmes have been found to produce more accurate pedigrees and more appropriate management decisions. (III)

Recommendations

Family history-taking and initial assessment in primary care

- When a person with no personal history of breast cancer 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. **[2004]**
- Healthcare professionals should respond to a person who presents with concerns but should not, in most instances, actively seek to identify people with a family history of breast cancer. **[2004]**
- In some circumstances, it may also be clinically relevant to take a family history, for example, for women older than age 35 years using an oral contraceptive pill or for women being considered for long-term HRT use. **[2004]**
- A person should be given the opportunity to discuss concerns about their family history of breast cancer if it is raised during a consultation. **[2004]**
- A second-degree family history (that is, including aunts, uncles and grandparents) should be taken in primary care before explaining risks and options. **[2004]**
- A second-degree family history needs to include paternal as well as maternal relatives. **[2004]**
- Asking people to discuss their family history with relatives is useful in gathering the most accurate information. **[2004]**
- Tools such as family history questionnaires and computer packages exist that can aid accurate collection of family history information and they should be made available. **[2004]**
- For referral decisions attempts should be made to gather as accurate information as possible on:
    - age of diagnosis of any cancer in relatives
    - site of tumours
    - multiple cancers (including bilateral disease)
    - Jewish ancestry[4]. **[2004]**

Family history-taking in secondary care

- A family history should be taken when a person with no personal history of breast cancer presents with breast symptoms or has concerns about relatives with breast cancer. **[2004]**

[4] Women with Jewish ancestry are around 5-10 times more likely to carry *BRCA1* or BRCA2 mutations than women in non-Jewish populations.

- A third-degree family history should be taken in secondary care where possible and appropriate. **[2004]**
- Tools such as family history questionnaires and computer packages exist that can aid accurate collection of family history information and risk assessment and they should be made available. **[2004]**

Family history-taking in tertiary care

- A third-degree family history should be taken in tertiary care for a person with no personal history of breast cancer, if this has not been done previously. **[2004]**
- For accurate risk estimation the following are required:
  - age of death of affected and unaffected relatives
  - current age of unaffected relatives. **[2004]**
- In general, it is not necessary to validate breast cancer only histories (via medical records/cancer registry/death certificate). **[2004]**
- If substantial management decisions, such as risk-reducing surgery, are being considered and no mutation has been identified, clinicians should seek confirmation of breast cancer only histories (via medical records/cancer registry/death certificates). **[2004]**
- Where no family history verification is possible, agreement by a multidisciplinary team should be sought before proceeding with risk-reducing surgery. **[2004]**
- Abdominal malignancies at young ages and possible sarcomas should be confirmed in specialist care**. [2004]**

2.5 Family history and carrier probability

Identifying the disease-predisposing mutation in a family facilitates follow-up (predictive) genetic testing for unaffected at risk relatives. This assists the development of personalised healthcare for cancer risk management, such as surveillance, risk-reducing surgery, chemoprevention options and lifestyle modification.

The presence of other malignancies such as ovarian/prostate/pancreatic cancer in a family in addition to breast cancer increases the likelihood of identifying a *BRCA1*/2 mutation carriers. Likewise the presence of early onset sarcoma and childhood cancers such as adrenal carcinoma make the possibility of a *TP53* mutation more likely.

CG41 did not specify how carrier probability should be estimated. Several cancer risk and carrier probability assessment tools have been published. These are widely, but variably used in clinical practice. Some family structures cannot be usefully interrogated with every assessment model, including the ability to include cancers in relatives other than first or second-degree to the assessed individual. It is important to note that studies reporting model validation have mostly been based on families with carrier probabilities above 10% and the performance of these models in families with lower carrier probabilities is not known.

The criteria for referral to tertiary care are based on the carrier probability. However, it is not expected that health care practitioners in secondary care should utilise pedigree analysis programmes such as BOADICEA for estimating carrier probabilities. No simple, criterion-based carrier probability algorithm has been published, but the Manchester score method allows a straightforward criterion-based scoring of a pedigree. The resulting score corresponds to an approximate carrier probability.

Clinical Question: What are the optimal methods for assessing the carrier probability of people (whether or not they have a personal history of breast cancer) at different thresholds for genetic testing in women and men at risk of familial breast cancer?

Clinical Evidence (2013) (see also full evidence review)

Study quality

Evidence came from 26 studies of carrier probability models (BOADICEA, BRCAPRO, IBIS, MYRIAD, MANCHESTER, PENN, PENN II and FHAT) or risk counsellors (Antoniou, *et al.,* 2006, 2008; Barcenas, *et al.,* 2006; Berry, *et al.,* 2002; Bodmer, *et al.,* 2006; Capalbo, *et al.,* 2006; de la Hoya, *et al.,* 2003; Euhus, *et al.,* 2002; Evans, *et al.,* 2004, 2009; Fasching, *et al.,*, 2007; James, *et al.,* 2006; Kang, *et al.,* 2006; Kurian, *et al.,* 2009; Lindor, *et al.,* 2010; Oros, *et al.,*, 2006; Ottini, *et al.,* 2003; Panchal, *et al.,* 2008; Parmigiani, *et al.,* 2007; Rao, *et al.,* 2009; Rosati, *et al.,* 2004; Roudgari, *et al.,* 2008; Simard, *et al.,* 2007; Teller, *et al.,* 2010; Vogel, *et al.,*, 2007 and Zanna, *et al.,* 2010). The participants in these studies were people tested for *BRCA1* and/or *BRCA2* mutations identified from the records of clinical genetics services. Referral for these genetic tests would depend on an initial assessment of carrier probability, so these studies excluded people whose carrier probability was judged too low for them to have genetic tests. This limits the applicability of this evidence in patients with low carrier probability.

There were some differences between studies in the way the carrier probability models had been used. Some studies estimated missing values (such age or year of death), whilst others excluded these cases. Some did not state the model version used: many of the models have been updated over time to improve accuracy or modified to better reflect local populations. The sensitivity of the reference standard (genetic tests for *BRCA1* and *BRCA2* mutations) is likely to have improved over the study periods (2002 to 2010), which in turn could affect the accuracy of the carrier probability models.

Evidence statements

The area under the ROC curve (AUROC) measures the discrimination of a carrier probability model (its ability to separate mutation carriers from non carriers): where 1 is perfect discrimination and 0.5 is no better than chance. There was moderate quality but consistent evidence that carrier prediction models performed significantly better than chance with typical AUROC values between 0.7 and 0.8 for the BOADICEA, BRCAPRO, IBIS, MYRIAD, MANCHESTER, PENN, PENN II and FHAT models. The estimated AUROC for risk counsellors ranged from 0.69 to 0.70 (Table 2.2).

Calibration refers to how well a model's predicted carrier probability relates to the true carrier probability within a group of patients. Antoniou, *et al.,* (2008) compared the calibration of the BOADICEA, BRCAPRO, IBIS, MANCHESTER and MYRIAD models using data from six UK cancer genetic clinics. Calibration was tested by comparing predicted and observed mutations within groups defined by their predicted carrier probability. BOADICEA was the best calibrated model – being the only one of the five models in which the total number of observed mutations was not significantly different to the total number of predicted mutations.

Table 2.2: Area under the ROC curve (95% confidence interval) of carrier probability models for *BRCA1* or *BRCA2* mutation

Study	Prevalence	BOADICEA	BRCAPRO	IBIS	MYRIAD	MANCHESTER	PENN	PENN II	FHAT	Risk Counsellor
Antoniou *et al.,* 2006	0.18	0.81 (0.73 – 0.90)	0.83 (0.75 –0.91)							
Antoniou *et al.,* 2008	0.19	0.77 (0.74 – 0.80)	0.76 (0.73 – 0.79)	0.74 (0.71 - 0.77)	0.72 (0.69 – 0.75)	0.75 (0.72 – 0.77)				
Panchal *et al.,* 2008	0.33	0.74 (0.67 – 0.80)	0.76 (0.70 – 0.82)	0.47 (0.28 – 0.69)	0.76 (0.71 – 0.82)	0.68 (0.60 – 0.76)		0.74 (0.67 – 0.80)	0.74 (0.66 – 0.80)	
Parmigiani *et al.,* 2007 - population based.	0.04		0.85 (0.81 – 0.88)		0.79 (0.72 – 0.86)		0.75 (0.69 – 0.81)		0.79 (073 – 0.85)	
Parmigiani *et al.,* 2007 - high risk	0.28		0.76 (0.73 – 0.79)		0.71 (0.68 – 0.74)		0.73 (0.70 – 0.76)		0.71 (0.68 – 0.74)	
Barcenas *et al.,* 2006	0.19	0.78 (0.72 – 0.85)	0.80 (0.75 – 0.86)		0.78 (0.72 – 0.84)					
de la Hoya *et al.,* 2003	0.34				0.82 (0.73 – 0.89)		0.77 (0.68 – 0.85)			0.69 (0.60 – 0.78)
Euhus *et al.,* 2002	0.43		0.71							0.70
Evans *et al.,* 2004	0.09		0.60 (0.46 – 0.74)		0.71 (0.60– 0.83)	0.77 (0.67 – 0.88)				
James *et al.,* 2006	0.27		0.78 (0.72 – 0.85)		0.74 (0.67 – 0.81)	0.70 (0.62 – 0.77)	0.73 (0.67 – 0.80)		0.68 (0.61 – 0.75)	
Kang *et al.,* 2006	0.14		0.74 (0.67 – 0.81)		0.75 (0.68 – 0.83)	0.76 (0.69 – 0.83)	0.76 (0.69 – 0.83)			
Kurian *et al.,* 2009 -NHW	0.06	0.83 (0.63 – 0.93)	0.83 (0.63 – 0.93)							
Kurian *et al.,* 2009 -Hispanic	0.08	0.56 (0.43 – 0.68)	0.58 (0.45 – 0.70)							
Kurian *et al.,* 2009 -African American	0.05	0.75 (0.60 – 0.85)	0.74 (0.59 – 0.85)							
Lindor *et al.,* 2010	0.30		0.76 (0.70 – 0.82)		0.71 (0.64 – 0.77)		0.72 (0.64 – 0.78)	0.79 (0.72 – 0.84)		
Oros *et al.,* 2006	0.43		0.81		0.74	0.79			0.80	
Rao *et al.,* 2009	0.15		0.73 (0.64 – 0.811)		0.74 (0.65 – 0.84)					
Roudgari *et al.,* 2008	0.51	0.68		0.73		0.76				
Simard *et al.,* 2007	0.29				0.75 (0.66 – 0.83)	0.89 (0.84 – 0.95)				
Teller *et al.,* 2010	0.28				0.68			0.72		
Zanna *et al.,* 2010	0.10		0.82		0.61				0.72	

Cost effectiveness evidence (2013)

A literature review of published cost-effectiveness analysis did not identify any relevant papers. No further health economic analysis was undertaken as it was difficult to identify the consequences to patients of selecting a particular method of assessing carrier probability. In addition, the choice of one method over another was considered unlikely to yield significant health benefits.

Recommendations

- When available in secondary care use a carrier probability calculation method with demonstrated acceptable performance (calibration and discrimination) as well as family history to determine who should be offered referral to tertiary care. Examples of acceptable methods include BOADICEA and the Manchester scoring system. **[new 2013]**
- In tertiary care use a carrier probability calculation method with demonstrated acceptable performance (calibration and discrimination) to assess the probability of a *BRCA1* or *BRCA2* mutation. Examples of acceptable methods include BOADICEA and the Manchester scoring system). **[new 2013]**
- If there are problems with using or interpreting carrier probability calculation methods use clinical judgement when deciding whether to offer genetic testing. **[new 2013]**

Linking Evidence to Recommendations

The aim of this topic was to determine the optimal methods for assessing the carrier probability of a person at different thresholds for genetic testing in women and men at risk of familial breast cancer. This topic was updated because previous guidance included no advice on which methods or tools to use to assess carrier probability.

The GDG considered the ability of different methods to discriminate carriers from non-carriers and to predict mutation carrier probability as the most important outcomes for this question, as they were fundamental parameters needed to estimate the performance of any carrier probability method. The GDG noted that evidence was reported for each of these outcomes. As this was a diagnostic topic, QUADAS was used to assess the quality of the evidence, which indicated that the overall quality of the evidence was moderate. Meta-analysis was not done as there was considerable unexplained variation between results from the individual studies.

The GDG noted that the evidence about the performance of mutation carrier probability models in people with very low carrier probability was limited. However, the GDG felt there was a sufficient range of carrier probability within the included study populations to estimate carrier prediction model performance at the thresholds used in practice. The GDG also agreed that calculating a carrier probability in the lower thresholds (<20%) would be difficult to do accurately without the use of a mutation carrier probability model and therefore it was unlikely that risk counsellors would assess carrier probability without using a model. As such the GDG determined that it was unhelpful to consider the evidence on risk counsellors in isolation.

The GDG considered, based on the evidence, that all the mutation carrier probability models investigated had adequate discrimination and calibration to be useful. The GDG acknowledged that recommending the use of a carrier probability calculation method could reduce the current variation in practice and bring consistency to families who may benefit a from genetic testing, as all eligible people will have their risk assessed. It was the opinion of the GDG that this could also improve the targeting of limited resources to the most eligible

people. At the same time, the GDG acknowledged that over reliance by healthcare professionals on carrier probability calculation methods could reduce clinical judgement.

The GDG were also aware that due to the variety of different carrier probability calculation methods currently available, a recommendation for their use could lead to variation in which specific method was used. However, they felt that recommending calculation methods that have demonstrated acceptable performance would limit this variation. The GDG also noted that if these calculation methods are used without confirmation of cancer diagnoses in the family they may give an inaccurate result.

The GDG noted there were only small differences in performance between existing methods of assessing carrier probability and so they were unable to recommend one method over another. However for illustrative purposes, the GDG agreed to cite BOADICEA and the Manchester Score as examples of models in common use in the UK. The BOADICEA method is a computer-based tool whereas the Manchester Score can be calculated on paper and so provides healthcare professionals the option of either approach to calculating carrier probability. Because of the lack of evidence for this topic GDG did not wish to prohibit healthcare professionals from using other methods with demonstrated acceptable performance should they so wish.

The GDG noted that no relevant economic evaluations had been identified and no additional economic analysis had been undertaken in this area. It was the opinion of the GDG that there may be potential cost savings made as people will be appropriately assessed and classified for genetic testing. The GDG also noted that there would not be any additional costs in acquiring the calculation tools, and the number of families being seen by a genetic counsellor would not increase. However there may be additional costs in training healthcare professionals to use these tools.

The GDG also acknowledged that existing carrier probability calculation methods do not consider particular data items, such as tumour pathology. Therefore the GDG decided to recommend further research into the development and validation of models for calculating carrier probability which incorporate additional data, such as the molecular pathology of tumours and the prevalence of mutations in different ethnic groups.

Research Recommendation

- Further research is recommended into developing and validating models for calculating carrier probability which incorporate additional data, such as the molecular pathology of tumours and the prevalence of mutations in different ethnic groups**. [new 2013]**

2.6 Communicating cancer risk and carrier probability

The communication of information on cancer risk and carrier probability is not straightforward. There is a degree of uncertainty with respect to the probability of inheriting a predisposing genetic mutation, of gene penetrance and hence of developing cancer. Consequently the needs and expectations of people seeking advice may not be in line with available knowledge.

Information can be provided in several ways and optimal method of communicating a person's risk is uncertain. Although complex, communicating numerical risk information is necessary as it forms the basis for offering risk management (e.g. risk-reducing surgery or surveillance) and decision making about preventive strategies.

People attending cancer genetics clinics usually want to discuss their family history, cancer risks and risk management options. Individuals' beliefs about inheritance and risk may interfere with assimilation of information and the presence of a family history of cancer may result in a strongly held perception that their risk is high.

Clinical Evidence (2004) (see also full evidence review)

Evidence relating to the communication of breast cancer risk in women with a family history of breast cancer is limited, relates to mainly qualitative research studies and has addressed various aspects concerning how cancer risk is communicated in this population of women.

Two studies have evaluated different risk information formats (Hallowell, *et al.,* 1997a,b; Schapira, *et al.,* 2001), and 7 further studies have investigated women's recall of risk information and whether written summaries have aided this, and the observed problems which clinicians encounter in translating scientific knowledge into their clinical management at a hereditary cancer clinic (Hallowell, *et al.,* 1997a,b; Hallowell, *et al.,* 1998; Sachs, *et al.,* 2001, Cull, *et al.,* 1999, Evans, *et al.,* 1994, Hopwood, *et al.,* 1998, Watson, *et al.,* 1999).

A literature review of studies which have assessed the process of risk communication for familial cancer has concluded that there is no clear evidence on how to effectively communicate cancer risk information and to ensure that risk estimates are understood.

Evidence Statements (2004)

There is no clear evidence on how to effectively communicate cancer risk information and to ensure that risk estimates are understood. (IV)

Risk communication improves the accuracy of the woman's perceived risk. (IV)

Qualitative studies have indicated that in women who attended genetics clinics, many found personal risk information useful. (IV)

There is some evidence that numerical risk values are preferred over risk categories. (IV)

The use of a written summary of the consultation reinforces risks information and enhances recall. (IV)

Recommendations

- People should be offered a personal risk estimate but information should also be given about the uncertainties of the estimation. **[2004]**
- When a personal risk value is requested, it should be presented in more than one way (for example, a numerical value, if calculated, and qualitative risk). **[2004]**
- People should be sent a written summary of their consultation in a specialist genetic clinic, which includes their personal risk information. **[2004]**

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3 Information and support

People who are concerned about a family history of breast cancer may require information to help them deal with the complex medical and social choices linked with different levels of breast cancer risk management options, and support to cope with the associated uncertainty and anxiety.

Breast cancer risk assessment is currently carried out in secondary care in breast cancer family history clinics and tertiary care genetic centres. However, the first contact with the health service is usually through primary care where specialist knowledge regarding risk assessment in less likely to be available.

The availability of information and support to people regardless of their risk level is important.

Clinical evidence (2004) (see also full evidence review)

These recommendations are based on the consensus of the guideline development group, and reflect good clinical professional practice. They may seem self-evident but it was thought worthwhile to reiterate them.

Recommendations

- 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. **[2004]**
- To ensure a patient–professional partnership, patients should be offered individually tailored information, including information about sources of support (including local and national organisations). **[2004]**
- Tailoring of information should take into account format (including whether written or taped) as well as the actual content and form that should be provided (see box 3.1). **[2004]**
- Standard information should be evidence based wherever possible, and agreed at a national level if possible (NICE's Information for the public provides a good starting point).**[2004]**
- Standard information should not contradict messages from other service providers, including commonly agreed information across localities. **[2004]**

Box 3.1 Information provision for people with concerns about familial breast cancer risk

Standard written information for all people

- Risk information about population level and family history levels of risk, including a definition of family history.
- The message that if their family history alters, their risk may alter.
- Breast awareness information.
- Lifestyle advice regarding breast cancer risk, including information about:
  - HRT and oral contraceptives (women only)
  - lifestyle, including diet, alcohol, etc
  - breastfeeding, family size and timing (women only).
- Contact details of those providing support and information, including local and national support groups.
- People should be informed prior to appointments that they can bring a family member/friend with them to appointments.
- Details of any trials or studies that may be appropriate.

For people cared for in primary care

- Standard written information (as above).
- Advice to return to discuss any implications if there is a change in family history or breast symptoms develop.

For people being referred to secondary care

- Standard written information (as above).
- Information about the risk assessment exercise that will take place and advice about how to obtain a comprehensive family history if required.
- Information about potential outcomes depending on the outcome of the risk assessment (including referral back to primary care, management within secondary care or referral to a specialist genetics service) and what may happen at each level.

For people being referred back to primary care

- Standard written information (as above).
- Detailed information about why secondary or a specialist genetics service are not needed.
- Advice to return to primary care to discuss any implications if there is a change in family history change or breast symptoms develop.

For people being cared for in secondary care

- Standard written information (as above).
- Details of the risk assessment outcome, including why they are not being referred to a specialist genetics service.
- Details of surveillance options including risk and benefits.

For people being referred to tertiary care

- Standard written information (as above)
- Details of the risk assessment outcome including why they are being referred to a specialist genetic service
- Details of surveillance options including risk and benefits
- Details of what should be expected in a specialist genetics service, including counselling and genetic testing

For people being cared for in tertiary care

- Standard written information (as above).
- Information about hereditary breast cancer.
- Information about genetic testing, both predictive testing and mutation finding, including details of what the tests mean and how informative they are likely to be, and the likely timescale of being given the results.
- Information about the risks and benefits of risk-reducing surgery when it is being considered, including both physical and psychological impact.

4 Care of people in primary care

The objectives of this chapter are to outline the role of primary care practitioners in:

- ensuring that people with concerns about their family history of breast cancer have an appropriate risk assessment and care plan
- offering the information and support people need.

4.1 Care and management in primary care

People with a family history of breast cancer may have concerns about their cancer risk and may anticipate that the primary care professionals will address these concerns.

Initially, primary care has an important role in taking a family history to inform a personal risk assessment (see section 2.3). The majority of people with a family history of breast cancer will not be at substantially increased risk. In these circumstances, discussions about breast awareness, relevant lifestyle factors and national breast screening programmes[6] are important.

Primary care professionals have an important role in preparing individuals and providing them with information about what to expect from referral and supporting them afterwards with the implications and ongoing management of their familial breast cancer risk.

Clinical Evidence (2004) (see also full evidence review)

Several studies have reported on a wide range of issues relating to the management of women with a family history of breast cancer in primary care. These are described in detail in other relevant sections of the document (see family history taking, patient education and information).

The evidence from these has informed the recommendations in this chapter.

Recommendations

Primary care management

- People without a personal history of breast cancer can be cared for in primary care if the family history shows only one first-degree or second-degree relative diagnosed with breast cancer at older than age 40 years[7], provided that none of the following are present in the family history:
  - bilateral breast cancer
  - male breast cancer
  - ovarian cancer
  - Jewish ancestry
  - sarcoma in a relative younger than age 45 years
  - glioma or childhood adrenal cortical carcinomas
  - complicated patterns of multiple cancers at a young age

[6] 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)

[7] In most cases this will equate to a less than 3% 10 year risk of breast cancer at aged 40.

- paternal history of breast cancer (two or more relatives on the father's side of the family). **[2004]**

- People who do not meet the criteria for referral should be cared for in primary care by giving standard written information (see box 3.1). **[2004]**

Referral from primary care

- People without a personal history of breast cancer who meet the following criteria should be offered referral to secondary care: **[2004]**
  - one first-degree female relative diagnosed with breast cancer at younger than age 40 years
    or
  - one first-degree male relative diagnosed with breast cancer at any age
    or
  - one first-degree relative with bilateral breast cancer where the first primary was diagnosed at younger than age 50 years
    or
  - two first-degree relatives, or one first-degree **and** one second-degree relative, diagnosed with breast cancer at any age
    or
  - one first-degree or second-degree relative diagnosed with breast cancer at any age **and** one first-degree or second-degree relative diagnosed with ovarian cancer at any age (one of these should be a first-degree relative)
    or
  - three first-degree or second-degree relatives diagnosed with breast cancer at any age.**[2004]**
- Advice should be sought from the designated secondary care contact if any of the following are present in the family history in addition to breast cancers in relatives not fulfilling the above criteria:
  - bilateral breast cancer
  - male breast cancer
  - ovarian cancer
  - Jewish ancestry
  - sarcoma in a relative younger than age 45 years
  - glioma or childhood adrenal cortical carcinomas
  - complicated patterns of multiple cancers at a young age
  - paternal history of breast cancer (two or more relatives on the father's side of the family). **[2004]**
- Discussion with the designated secondary care contact should take place if the primary care health professional is uncertain about the appropriateness of referral because the family history presented is unusual or difficult to make clear decisions about, or where the person is not sufficiently reassured by the standard information provided. **[2004]**
- Direct referral to a specialist genetics service should take place where a high risk predisposing gene mutation has been identified (For example. *BRCA1*, *BRCA2* or *TP53*). **[2004]**

4.2 Patient education and information

The provision of clear information on how a person's risk has been assessed and its implications is important to help people obtain a realistic understanding of their breast cancer risk and the significance of their family history.

A perceived high risk may be attributed to cancers in the family that are not associated with a possible genetic predisposition, causing unnecessary anxiety and demands for surveillance (see section 2.5). In some situations people may have expectations of health services that are inconsistent with what they are likely to receive.

Women may express concerns about the oral contraceptive (OC) pill, HRT and other possible risk factors because there has been breast cancer in the family. Concerns may also arise during routine collection of family history in primary care, for example, at registration with General Practice.

Clinical evidence (2004) (see also full evidence review)

Evidence from two qualitative studies and one survey has shown that women with a family history of breast cancer have unmet needs for information, support and reassurance either in the primary care setting (Chalmers, *et al.,* 1996; Grande, *et al.,* 2002), or whilst awaiting specialist genetics consultations having been referred by their GP (Andermann, *et al.,* 2001).

The GP's role in providing information and reassurance was seen to be extremely important for these women, particularly for those who are not referred to secondary care, as the GP may be their only source of information and advice.

A further study which developed and evaluated a research-based leaflet for women with a family history of cancer for use in a primary care setting found that it was effective in meeting women's information (Andermann, *et al.,* 2002).

Recommendations

Information for women who are being referred

- Women who are being referred to secondary or tertiary care should be provided with written information about what happens at this stage (see box 3.1). **[2004]**

Information and ongoing support for women who are not being referred

- Support mechanisms (e.g. risk counselling, psychological counselling, and risk management advice) need to be identified and should be offered to women not eligible for referral and/or surveillance on the basis of age or risk level who have ongoing concerns. **[2004]**

Support for primary care

- Support is needed for primary care health professionals to care for women with a family history of breast cancer. Essential requirements for support for primary care are:
  - a single point and locally agreed mechanism of referral for women identified as being at increased risk
  - educational materials about familial breast cancer
  - decision-support systems
  - standardised patient information leaflets
  - a designated secondary care contact to discuss management of 'uncertain' cases. **[2004]**

References (2004)[8]

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Andermann AA, Watson EK, Lucassen AM, Austoker J. (2001) The Opinions, Expectations and Experiences of Women with a Family History of Breast Cancer Who Consult Their GP and Are Referred to Secondary Care. Community Genet; 4 (4):239-43

Chalmers, K., Thomson, K. (1996). Coming to terms with the risk of breast cancer: Perceptions of women with primary relatives with breast cancer. Qualitative Health Research, 6:256-282.

[8] This is the complete reference list for the 2004 recommendations. Not all references are citied in the corresponding clinical evidence summary paragraphs.

5 Care of people in specialist (secondary and tertiary) care

The aim of this chapter is to specify the referral criteria to the appropriate setting for people with an increased risk due to family history but with no personal experience of breast cancer. It also provides an outline specification for the services they should expect including genetic counselling. For those with a personal history of breast cancer this chapter only defines criteria for management in tertiary care.

5.1 Care and management approach

Existing practice in the 1990's and early 2000's supported a three tiered approach to managing breast cancer risk. This approach was also supported by the Harper report, Calman report and NHS Cancer plan from 2001. It was also supported by the three tiers of medical care; primary, secondary and tertiary care. The main need for management in secondary care was for surveillance of those at moderate risk of breast cancer who would not qualify for genetic testing or risk-reducing surgery.

The decision to base moderate risk at a threshold of 3% ten-year risk at age 40 years (or 17% lifetime risk) was to identify a level of risk equivalent to the average population risk of a 50 year old women eligible for breast screening through the national breast screening programmes.

The 30% lifetime risk for breast cancer equating to high risk was determined as a reasonable threshold for offering risk-reducing surgery. The genetic testing threshold determines the other criterion for the high risk category.

Since 2004 the risk threshold has since been supported by the favourable results of the FH01 study which used the same threshold as NICE guidance.

Clinical Evidence (2004) (see also full evidence review)

The recommendations in section 5.1 are based on the consensus of the guideline development group, and reflect good clinical professional practice

Recommendations

Care of people in secondary care

- Care of people in secondary care (such as a breast care team, family history clinic or breast clinic) should be undertaken by a multidisciplinary team. It should include the following:
  - written protocols for management
  - central, standardised resources
  - mammographic surveillance available to standard of the national breast screening programmes[9]
  - access to surveillance (see section 7.2)

[9] 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)

- access to a team offering risk-reducing surgery
- standardised written information
- designated/lead clinicians
- a designated contact for primary care
- a designated contact in tertiary care
- audit
- clinical trials access
- access to psychological assessment and counselling
- information about support groups and voluntary organisations
- administrative support. **[2004]**

Management in secondary care

- People who meet the following criteria should be offered secondary care and do not require referral to tertiary care: **[2004]**
  - one first-degree relative diagnosed with breast cancer at younger than age 40 years

  or
  - two first-degree or second-degree relatives diagnosed with breast cancer at an average age of older than 50 years

  or
  - three first-degree or second-degree relatives diagnosed with breast cancer at an average age of older than 60 years

  or
  - a formal risk assessment (usually carried out in tertiary care) or a family history pattern is likely to give risks of greater than 3–8% risk in the next 10 years for women aged 40 years, or a lifetime risk of 17% or greater but less than 30%[10]

provided that none of the following are present in the family history:

- bilateral breast cancer
- male breast cancer
- ovarian cancer
- Jewish ancestry
- sarcoma in a relative younger than 45 years of age
- glioma or childhood adrenal cortical carcinomas
- complicated patterns of multiple cancers at a young age
- very strong paternal history (four relatives diagnosed at younger than 60 years of age on the father's side of the family). **[2004]**

- People whose risk does not meet the criteria for referral to secondary care (section 4.1) can be referred back to primary care:
  - with appropriate information being offered (see box 3.1), **and**
  - support mechanisms (For example, risk counselling, psychological counselling, and risk management advice) need to be identified and should be offered to people not eligible for referral and/or surveillance on the basis of age or risk level who have ongoing concerns. **[2004]**

Referral to tertiary care

- People who meet the following referral criteria should be offered a referral to tertiary

[10] For the purpose of these calculations, a women's age should be assumed to be 40 for a women in her forties. A 10-year risk should be calculated for the age range 40-49.

care. **[2004]**

At least the following female breast cancers only in the family

- two first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 50 years (at least one must be a first-degree relative) **[2004]**

or

- three first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years (at least one must be a first-degree relative) **[2004]**

or

- four relatives diagnosed with breast cancer at any age (at least one must be a first-degree relative) **[2004]**

or

Families containing one relative with ovarian cancer at any age and, on the same side of the family

- one first-degree relative (including the relative with ovarian cancer) or second-degree relative diagnosed with breast cancer at younger than age 50 years. **[2004]**

or

- two first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years. **[2004]**

or

- another ovarian cancer at any age. **[2004]**

or

Families affected by bilateral cancer (each breast cancer has the same count value as one relative)

- one first-degree relative with cancer diagnosed in both breasts at younger than an average age 50 years. **[2004]**

or

- one first-degree or second-degree relative diagnosed with bilateral cancer **and** one first or second-degree relative diagnosed with breast cancer at younger than an average age 60 years. **[2004]**

or

Families containing male breast cancer at any age and, on the same side of the family, at least:

- one first-degree or second-degree relative diagnosed with breast cancer at younger than age 50 years. **[2004]**

or

- two first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years. **[2004]**

or

A formal risk assessment has given risk estimates of

- a 10% or greater chance of a gene mutation being harboured in the family. (see section 6.3) **[new 2013]**

or

- a greater than 8% risk of developing breast cancer in the next 10 years. **[2004]**

or

- a 30% or greater lifetime risk of developing breast cancer. **[2004]**

or

- A family Manchester score of 15 or more **and**:
  - an affected first-degree relative **or,**
  - an affected second-degree paternal relative. (see section 6.3) **[new 2013]**
- Clinicians should seek further advice from a specialist genetics service for families containing any of the following, in addition to breast cancers:
  - Jewish ancestry **[2004]**
  - sarcoma in a relative younger than 45 years of age **[2004]**
  - glioma or childhood adrenal cortical carcinomas **[2004]**
  - complicated patterns of multiple cancers at a young age **[2004]**
  - very strong paternal history (four relatives diagnosed at younger than 60 years of age on the father's side of the family) **[2004]**
  - triple negative breast cancer under the age of 40 years**[new 2013]**
- The management of a high-risk people may take place in secondary care if they do not want genetic testing or risk-reducing surgery and do not wish to be referred to a specialist genetics service. **[2004]**
- Following initial consultation in secondary care, written information should be provided to reflect the outcomes of the consultation (see box 3.1). **[2004]**

Care of people in tertiary care

- Care of people referred to tertiary care should be undertaken by a multi-disciplinary team. In addition to having access to the components found in secondary care it should also include the following:
  - clinical genetic risk assessment
  - verification for abdominal malignancies and possible sarcomas. **[2004]**

5.2 Genetic counselling for people with no personal history of breast cancer

Genetic counselling describes the consultation between an individual (or individuals) with a family history of breast cancer and a person trained in genetic aspects of the risk of occurrence of breast cancer in the family.

Genetic counselling aims to:

- help the individual comprehend the medical facts, and specifically how inheritance contributes to the risk of developing breast cancer
- provide information about their personal risk of cancer, according to how much the individual wishes to know
- discuss the available options for risk management
- choose a personal course of action that seems most appropriate in view of the level of risk, personal preferences, family goals, ethical and religious standards
- help the individual adjust to the risk and its implications

The outcomes of cancer genetic counselling (both for risk assessment and genetic testing) have been assessed largely in terms of the accuracy of counselee's risk perceptions, mental health, attitudes to and psychosocial outcomes of genetic testing and to a lesser extent, health care behaviour.

People often have inaccurate perceptions of personal and population risks of developing breast cancer prior to genetic counselling. The risks are often overestimated and this may

cause increased anxiety and lead to unrealistic expectations of access to surveillance, genetic testing and cancer prevention.

Clinical Evidence (2004) (see also full evidence review)

One meta-analysis and 1 systematic review have been identified, which have evaluated the impact of genetic counselling on psychological morbidity and breast cancer risk perception. Results from both studies consistently show that counselling does not have an adverse effect on psychological morbidity, with results in the meta-analysis indicating a statistically significant decrease in generalised anxiety. Both studies also showed that counselling improved accuracy of perceived breast cancer risk perception, with a statistically significant improvement observed in the meta-analysis. Studies included in the systematic review, however, showed that many women still overestimated their risk of breast cancer. Studies with longer-term follow-up and improved study design are required to confirm these findings.

Evidence Statements (2004)

Genetic counselling is associated with decreased anxiety, cancer worry and improvements in risk accuracy and knowledge, in the short term. (III)

Genetic counselling is not associated with increased anxiety. (III)

There is no difference in anxiety reduction and satisfaction between genetic counsellors compared to clinical geneticists. (IV)

Many women who mistakenly perceive their risk as high can be reassured that they are at not at such high levels of risk and need no further interventions. (IV)

Many women who consider taking a predictive test for *BRCA1*/2/*TP53* are enabled by genetic counselling to make an informed choice about whether or not to proceed with the test. (IV)

Recommendations

- Women with no personal history of breast cancer meeting criteria for referral to tertiary care should be offered a referral for genetic counselling regarding their risks and options. **[2004]**
- Women attending genetic counselling should receive standardised information beforehand describing the process of genetic counselling, information to obtain prior to counselling session, the range of topics to be covered and brief educational material about hereditary breast cancer and genetic testing. **[2004]**
- Predictive genetic testing should not be offered without adequate genetic counselling. **[2004]**

References (2004)[11]

Butow PN, Lobb EA, Meiser B, Barratt A, Tucker KM. Psychological outcomes and risk perception after genetic testing and counselling in breast cancer: a systematic review. Medical Journal of Australia 2003; 178: 77-81.

[11] This is the complete reference list for the 2004 recommendations. Not all references are citied in the corresponding clinical evidence summary paragraphs.

Meiser B,.Halliday JL. (2002) What is the impact of genetic counselling in women at increased risk of developing hereditary breast cancer? A meta-analytic review. Social Science & Medicine; 54:1463-70.

6 Genetic testing

The objective of this chapter is to identify when and how to offer genetic testing to people with:

- a family history but no personal history of breast cancer
- a family history and a personal history of breast cancer.

6.1 Genes associated with inherited breast cancer risk

At least five genes *(BRCA1, BRCA2, TP53, E-Cadherin, STK11)* are known to be associated with a high breast cancer risk (greater than 30% lifetime risk), but it is important to emphasise that these genes are not the only cause for familial breast cancer. It has been estimated that these genes explain about 25% of the excess familial risk of breast cancer. Most of the remainder is likely to be due to low to moderate penetrance alleles.

Of the known high risk genes, deleterious alleles of *BRCA1* and *BRCA2* are most common. Carriers of mutations in these genes have a high lifetime risk of breast cancer (variously estimated, depending on the context, as 65-85% for *BRCA1* and 40-85% for *BRCA2*). Both genes also confer a high risk of ovarian cancer (around 40-50% for *BRCA1*, 10-25% for *BRCA2*) as well as more moderately increased risks of other cancers. *BRCA1* and *BRCA2* mutations explain a considerable proportion of very high risk families (that is, families with four or more close relatives with breast cancer), particularly if there is also a family history of ovarian cancer or of male breast cancer. Mutations in these genes are however rare in the general population, and probably only account for about 2% of breast cancer cases overall.

Mutations in the *TP53* gene predispose to a very high risk of breast cancer, such that the majority of women are affected before the age of 50. Mutations in this gene also predispose to a range of other cancers including childhood sarcomas and brain tumours, and mutations are therefore usually identified when these cancers occur together in families, a syndrome known as Li-Fraumeni syndrome. Mutations in *TP53* are significantly rarer than *BRCA1* or *BRCA2* mutations.

When considering genetic testing, as well as testing for the well known *BRCA1*, *BRCA2* and *TP53* genes, it may be important to consider other genes associated with a potentially high risk of breast cancer such as *PTEN* and *E-cadherin*, where clinically appropriate.

Mutations in the *PTEN* gene are responsible for Cowden's syndrome, a very rare inherited disorder associated with an increased risk of breast cancer. Mutations in two other genes, *ATM* and *CHEK2*, are associated with moderate risks of breast cancer; clinical genetic testing for these genes has not been implemented.

Several hundred different mutations in *BRCA1* and *BRCA2* have been identified and these occur almost throughout their sequence. Although some mutations are found in multiple families, there is no one predominant mutation in the UK, as seen for example, in the case of cystic fibrosis. Consequently, testing for *BRCA1* and *BRCA2* mutations requires screening the entire coding sequence.

A different situation pertains in the Ashkenazi Jewish community. In this population, three "founder" mutations (two in *BRCA1*, one in *BRCA2*) are relatively common and explain almost all the high risk families due to these genes. Consequently, a much simpler more sensitive and specific test based on these mutations is available in this population.

Since mutations are uncommon unless there is a strong family history of breast and/or ovarian cancer, genetic testing is mostly targeted to such families. For genetic testing to be maximally informative, testing is usually carried out first on an individual affected with breast or ovarian cancer, who is likely to carry a mutation if one is present in the family. If a mutation is identified, other individuals in the family may be offered a "predictive" genetic test to determine whether or not they carry the mutation. Since this test is based on a single mutation, it is much more straightforward than the initial screen. In the absence of prior mutation finding in a family member, genetic testing is usually inconclusive.

6.2 Genetic testing for people with a family history but no personal history of breast cancer (2004)

In several situations where there is a high chance of a *BRCA1* or *BRCA2* mutation in the family there is either no available living affected family member or the affected family member is unwilling to provide a blood sample. Increasingly genetics departments are considering testing such individuals with a family history but no personal history of breast cancer as a negative test has utility in breast and ovarian cancer risk prediction for that individual. This may also provide a test for other family members if the genetic test is positive for either *BRCA1* or *BRCA2* and allows the individuals to undertake appropriate enhanced surveillance and risk reduction measures.

Clinical Evidence (2004) (see also full evidence review)

In terms of evidence for attitudes towards, and uptake of, genetic testing, identified studies generally lack rigorous design. The majority of studies are surveys carried out in the US, and some have small study samples.

Overall results, however, would indicate that expected and actual uptake of genetic testing in healthy men and women with a family history of breast and/or ovarian cancer is fairly high, indicating the acceptability of such programmes. Factors which appeared to positively influence uptake of genetic testing included a family history of breast/ovarian cancer, relief of uncertainty, older age, greater perceived risk, concerns about risks to children, cancer worry and need to learn more about surveillance options. Perceived risks of genetic testing included costs, anxiety about the possibility of a positive result, concerns about health insurance and the availability and demands of genetic testing programmes.

Overall, the evidence for psychosocial outcomes relating to genetic testing, again, lacks rigorous design, comprising mainly of surveys and observational studies, some with small study samples.

Findings for these studies indicate that, as would be expected, individuals who are found to be *BRCA1*/2 mutation carriers on disclosure of test results tend to have higher levels of psychological morbidity compared to non-carriers at post-test follow-ups (Lerman, *et al.,* 1996; Croyle, *et al.,* 1997; Meiser, *et al.,* 2002). There was some evidence that high-risk individuals who decline genetic testing were more vulnerable to an increase in depressive symptoms (Lerman, *et al.,* 1996; Lerman, *et al.,* 1998). Although most individuals cope well during the waiting period between blood sampling and results in terms of psychological functioning, some women and their partners experience increased anxiety and distress (Lodder, *et al.,* 1999; Broadstock, *et al.,* 2000). One qualitative study revealed the concerns of women deemed ineligible for genetic testing, in terms of their continued worries about their breast cancer risks despite their ineligibility and their frustration at the lack of information received (Bottorff, *et al.,* 2000).

Evidence statements (2004)

There are over 500 different mutations in *BRCA1* that have been reported. (IIb)

BRCA1/2 mutations account for the great majority of multiple case families with combinations of both breast and ovarian cancer and male and female breast cancer. (IV)

BRCA1/2 mutations account for less than one third of the inherited component of female breast cancer only families. (III)

There is some evidence to suggest that families that receive no results from a *BRCA1*/2 search/screen show some increased anxiety at a year. (III)

Normal practice in the UK is that all reported predictive testing is carried out within a protocol that has at least two sessions of genetic counselling. Shorter protocols have not been studied. (IV)

Once a mutation has been identified in a family this should provide near complete certainty about who has or has not inherited the high risk in the family. This allows unaffected individuals to undertake predictive genetic testing. (IV)

Tests aid women with decision making with regard to risk-reducing interventions (e.g. surgery) and surveillance, but may also give them greater certainty about the risks to themselves and their family. (IV)

There is limited evidence which shows that about half of women who have a positive (high risk) predictive test for *BRCA1* & 2 undertake risk-reducing surgery. The uptake in non-carriers is very low. (III/IV)

Thus far, there have been no results from large prospective well designed studies on the results of *BRCA1*/2 predictive testing. (IV) (note: the outcomes of the CR-UK study are awaited).

A negative predictive test for *BRCA1*/2 has been shown to reassure women in studies with short term follow-up. (IV)

A positive predictive test (high risk) result may lead to higher levels of psychological morbidity compared to a negative result, but is not increased over baseline. (IV)

Tests aid women with decision making with regard to risk-reducing interventions (e.g. surgery) and surveillance but may also give them greater certainty about the risks to themselves and their family. (IV)

BRCA1 & 2 testing in the UK has not identified particular hot spots or founder mutations. Mutations in *BRCA1 &* 2 are generally spread throughout the whole gene. (IV)

There are ethnic populations within the UK which have strong founder mutations such as the Jewish population. (IV)

Direct sequencing achieves high levels of sensitivity when used to identify sequence alterations. However, there are a number of other substantially cheaper options with virtually identical sensitivity such as MLPA, FAMA, DHPLC and DF. (III)

Techniques other than direct sequencing may need to be used to detect deletions. (III)

Summary of cost effectiveness evidence (2004) (see also full cost effectiveness evidence review)

It is difficult to draw definitive conclusions from the available data. It does appear however, as might be expected that testing of women at 'higher' risk is more cost effective than women at moderate or average risk. However there is lack of data, including test costs and accurate costs for other interventions.

Recommendations

- All eligible people should have access to information on genetic tests aimed at mutation finding. **[2004]**
- Pre-test counselling (preferably two sessions) should be undertaken. **[2004]**
- Discussion of genetic testing (predictive and mutation finding) should be undertaken by a healthcare professional with appropriate training. **[2004]**
- Eligible people and their affected relatives should be informed about the likely informativeness of the test (the meaning of a positive and a negative test) and the likely timescale of being given the results. **[2004]**

Mutation tests

- Tests aimed at mutation finding should first be carried out on an affected family member, where possible. **[2004]**
- If possible the development of a genetic test for a family should usually start with the testing of an affected individual (mutation searching/screening) to try to identify a mutation in the appropriate gene (such as *BRCA1*, *BRCA2* or *TP53*). (see also section 6.3) **[2004]**
- A search/screen for a mutation in a gene (such as *BRCA1*, *BRCA2* or *TP53*) should aim for as close to 100% sensitivity as possible for detecting coding alterations and the whole gene(s) should be searched. **[2004]**

6.3 Carrier probability at which genetic testing should be offered

In 2004 in order to reduce variation in clinical practice the carrier probability threshold for genetic testing *BRCA1* and *BRCA2* was set at 20%.

Since that time the cost of genetic testing and timeframe for reporting results has reduced considerably. Consequently many genetic centres have been able to lower the threshold for offering testing. This has led to further variation in clinical practice.

It is important to recognise that the threshold used has a direct impact on the number of people with deleterious gene alterations that can be identified. For example lowering the threshold for genetic testing will identify more people carrying deleterious gene alterations who could be suitable for risk reduction strategies.

BRCA1/2 gene testing may identify important aetiological factors in a woman's breast cancer that can inform her own future management as well as allow accurate predictive testing in her close relatives. Given that *BRCA1*/2 mutations will only explain a small proportion of all breast cancers as well as a small proportion of all women with a family history of breast cancer, it is not sensible to test all women with breast cancer. The stronger a woman's family history of cancer, the higher the chance she will harbour a pathogenic *BRCA1*/2 mutation.

The object of this section is to identify a threshold that will pick up a significant proportion of *BRCA1*/2 carriers whilst keeping specificity of testing as high as possible. Without the knowledge of a familial mutation, genetic testing in an unaffected relative is less clinically useful since it cannot exclude a mutation undetectable by current methods.

Clinical Question: What is the carrier probability at which genetic testing should be offered to people who are (a) unaffected but with a family history of breast/ovarian/related cancer and an affected relative willing to have a test; (b) unaffected with a family history and no living relative and (c) affected people?

Clinical Evidence (2013) (see also full evidence review)

Evidence Statements

There was no evidence comparing different carrier probability thresholds for genetic testing in terms of overall or disease specific survival or health related quality of life.

Cost effectiveness evidence for carrier probability at which genetic testing should be offered (2013) (see also full cost effectiveness evidence review)

A literature review of published cost effectiveness analyses identified four relevant papers (Balmana, *et al.,.,* 2004, Holland, *et al.,* 2009, Kwon, *et al.,* 2010a and 2010b). The results of these included studies are summarised in table 6.1.

Study quality and results

Four studies were included for this topic. All papers were deemed partially applicable to the guideline. The reasons for partial applicability were that the analyses were conducted in countries other than the UK or did not conform to one or more aspects of the NICE reference case. All papers were deemed to have very serious limitations.

Evidence statements

Balmana, *et al.,* (2004) showed that the cost-effectiveness ratio of their genetic counselling and screening program was £5267.17[12] per life-year gained. The model was sensitive to the prevalence of mutation carriers, the lifetime risk of breast cancer and the effectiveness of the screening, suggesting that testing for breast cancer in a high risk population may be cost-effective. Holland, *et al.,* (2009) suggested that at a 10% probability of mutation (the current US guideline), the test strategy generated 22.9 QALYs over a lifetime and cost £87,575.42[13] while the no-test strategy generated 22.7 QALYs and cost £86,833.26[14] The incremental cost-effectiveness ratio of the test strategy was £6679.48[15] and the differences between costs and effects were not substantial. The test strategy remained cost-effective to a probability of mutation of 0% as long as utility gained from a negative test result was 0.006 or greater.

[12] Converted from 2000 Euros using a PPP exchange rate of 0.88 then uprated by inflation factor of 139% (http://eppi.ioe.ac.uk/costconversion/default.aspx). Cost year of 2000 assumed as not stated in publication.
[13] Converted from 2006 U.S dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 108% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[14] Converted from 2006 U.S dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 108% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[15] Converted from 2006 U.S dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 108% (http://eppi.ioe.ac.uk/costconversion/default.aspx).

These results were sensitive to the frequency of inconclusive test results and utility gains from a negative test result. In a cohort of women with a personal history of ovarian cancer, Kwon, *et al.,* (2010a) showed that *BRCA* testing based on personal/family history and ancestry could prevent future cases in first-degree relatives with an ICER of £22,589.58[16] per year of life (LY) gained compared with the reference strategy. In a cohort of women with a personal history of breast cancer, Kwon, *et al.,* (2010b) showed that whilst *BRCA* mutation testing for all women with breast cancer who were younger than 50 years could prevent the highest number of breast and ovarian cancer cases, this was not cost-effective. Testing women with triple negative breast cancers who were younger than 40 years was cost-effective with an ICER of £4,796.64[17] per year of life gained (£5,495.06[18] per quality-adjusted life-year), and could reduce subsequent breast and ovarian cancer risks.

[16] Converted from 2008 U.S dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 103% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[17] Converted from 2009 U.S dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 102% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[18] Converted from 2009 U.S dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 102% (http://eppi.ioe.ac.uk/costconversion/default.aspx).

Table 6.1: Economic Evidence profile: Cost effectiveness of carrier probability at which genetic testing should be offered to people

Quality assessment			*Summary of findings*						
Study	*Limitations*	*Applicability*	*Population*	*Intervention*	*Comparator*	*Incremental cost (2011 £)*	*Incremental effects*	*ICER*	*Uncertainty*
Balmana, 2004	Very serious limitations [1]	Partially applicable [2]	Families having several relatives affected by breast cancer, frequently of an early onset, and might be associated with the presence of ovarian and male breast cancer. Age unknown	Genetic counselling (GC), genetic study of the index case (GSIC), clinical breast examination (CBE) and annual mammography (Mx) from 30 to 80 years or until breast cancer diagnosis	Determination of genetic status (GC and GSIC), no screening	£1010 [3] for screening compared to no screening	Life expectancy: 0.19 years gained with screening compared to no screening	Cost/LYG: £5267.17[4]	One-way sensitivity analysis showed that results were sensitive to the estimated probability of being a mutation carrier and thus detection rate of *BRCA* mutations, number of BCs without lymph node involvement as well as changes in life-time risk of BC in mutation carriers. No PSA reported.
Holland 2009	Very serious limitations [5]	Partially applicable [6]	35-year-old women with an associated family risk of breast and/or ovarian cancer 35-year-old women who were concerned about having a mutation	Genetic testing for *BRCA* mutation at age 35 followed by the possibility of preventative surgery if mutation was found	No genetic testing or prophylactic surgery but ongoing surveillance according to recommendations	£742.16 [7]	Utility scores: Screening (cumulative): 22.9 QALYs No screening (cumulative): 22.7 QALYs Incremental QALYs of screening: 0.2	£6679.48/QALY[8]	One-way sensitivity analysis and probabilistic sensitivity analysis performed and reported. Costs and effects of both strategies were found to be similar and not sensitive to parameter estimates. Probability of test-strategy cost-effective at 73 %

Quality assessment			Summary of findings						
Study	*Limitations*	*Applicability*	*Population*	*Intervention*	*Comparator*	*Incremental cost (2011 £)*	*Incremental effects*	*ICER*	*Uncertainty*
									when a QALY was valued at $100,000 and 70 % at $50,000.
Kwon 2010a	Very serious limitations [9]	Partially applicable [10]	Theoretical cohort of women in the general population with ovarian cancer	*BRCA* testing only if Ashkenazi Jewish, personal or family history of BC and/or OC (SGO criteria); *BRCA* testing only if invasive serous cancer; *BRCA* testing if any ovarian cancer	No *BRCA* mutation testing	Incremental cost compared to no testing[11]: SGO criteria: £735.87 Test serous: £1644.58 Test all: £2431.95	Life expectancy (years): Compared to no testing SGO criteria: 0.0326 Test serous: 0.0426 Test all: 0.0502 Utility score (QALYs): Compared to no testing SGO criteria: 0.0319 Test serous: 0.0415 Test all: 0.0491	Compared to no testing[12] SGO criteria: £23,049.58/ QALY Test serous: £92,503.83/ QALY Test all: £106,837.32 /QALY	Results were found stable over a wide range of plausible parameter estimates (including proportion of first-degree relatives undergoing testing and prophylactic surgery).
Kwon 2010b	Very serious limitations [13]	Partially applicable [14]	Theoretical cohort of women in the general population with breast cancer diagnosed at 50 or younger	Testing of women with medullary breast cancer younger than 50; Testing of women with any breast cancer younger than 40;	No testing	Compared to no testing[15] Medullary breast cancer: £57.33 Triple-negative BC <40: £199.25 Any BC <40: £634.80 Triple-	Life expectancy (years): Compared to no testing Medullary breast cancer: 0.011 Triple-negative BC <40: 0.040 Any BC <40: 0.103 Triple-negative BC <50: 0.121 Any BC <50: 0.178	Compared to no testing[16] Medullary breast cancer: £6075.33/Q ALY Triple-negative BC <40: £5495.06/Q	Results were found stable over a wide range of plausible parameter estimates.

Quality assessment			Summary of findings						
Study	Limitations	Applicability	Population	Intervention	Comparator	Incremental cost (2011 £)	Incremental effects	ICER	Uncertainty
				Testing of women with triple-negative BC younger than 40; Testing of women with triple-negative BC younger than 50		negative BC <50: £649.48 Any BC <50: £3018.79	Utility score (QALYs): Compared to no testing Medullary breast cancer: 0.008 Triple-negative BC <40: 0.032 Any BC <40: 0.086 Triple-negative BC <50: 0.098 Any BC <50: 0.127	ALY Any BC <40: £7688.89/QALY Triple-negative BC <50: £195.75/QALY Any BC <50: £78,935.88/QALY	

[1] Effectiveness data is based on one single hospital register; no cost year or discounting rates reported, exclusion and inclusion criteria unclear. Therefore the relevance of these results for informing the current guideline is limited.

[2] The analysis does not meet one or more aspects of the NICE reference case.

[3,4] Converted from 2000 Euros using a PPP exchange rate of 0.88 then uprated by inflation factor of 139% (http://eppi.ioe.ac.uk/costconversion/default.aspx). Cost year of 2000 assumed as not stated in publication.

[5] Effectiveness, cost and utility data is based on literature review (no methodology reported), exclusion and inclusion criteria unclear. Therefore the relevance of these results for informing the current guideline is limited.

[6] The analysis does not meet one or more aspects of the NICE reference case.

[7,8] Converted from 2006 U.S dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 108% (http://eppi.ioe.ac.uk/costconversion/default.aspx).

[9] Effectiveness, cost and utility data is based on literature review (no methodology reported), exclusion criteria and time horizon unclear. General population used for analysis, no separate analysis of family history, no risk groups reported. Therefore the relevance of these results for informing the current guideline is limited.

[10] The analysis does not meet one or more aspects of the NICE reference case.

[11,12] Converted from 2008 U.S dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 103% (http://eppi.ioe.ac.uk/costconversion/default.aspx).

[13] Effectiveness, cost and utility data is based on literature review (no methodology reported), exclusion criteria and time horizon unclear. Only ovarian cancer patients included in analysis. Therefore the relevance of these results for informing the current guideline is limited.

[14] The analysis does not meet one or more aspects of the NICE reference case.

[15,16] Converted from 2009 U.S dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 102% (http://eppi.ioe.ac.uk/costconversion/default.aspx).

Health Economics evaluation (see also full cost effectiveness evidence review)

The existing NICE Guideline (CG14) recommends that the carrier probability threshold at which genetic testing for mutations in *BRCA1* and *BRCA2* (or *TP53*) is offered to individuals affected by breast or ovarian cancer is set at 20%. The person's mutation probability is estimated by assessment of the family history. Genetic testing is offered in Tertiary Care if an affected individual's mutation risk exceeds the established threshold. Related to this is the recommendation that unaffected family members should be managed in Tertiary Care if their risk assessment gives a lifetime breast cancer risk equal to or greater than 30%, or the 10 year risk from 40 to 50 years is more than 8%. High-risk unaffected family members may harbour a substantial mutation carrier probability, depending on context. Currently there is no recommendation for offering tests to unaffected patients with a strong family history.

Since publication of CG14 in 2004, the threshold for testing has fallen, albeit inconsistently across all Tertiary Care Centres, with some adopting a 10% mutation probability for affected cases. Moreover, some centres now offer genetic testing to unaffected patients with a substantial risk of being mutation carriers, mostly in circumstances where no living affected family member is available to offer a direct diagnostic test. Changes in practice are related to declining costs of genetic testing and the increasing rapidity with which results can be achieved.

In view of these variations in practice, this topic is intended to assess the scope for changing the current probability threshold at which testing is offered to affected patients (male or female), that is with a current or previous diagnosis of breast or ovarian cancer. Furthermore, the economic evaluation will determine whether a probability threshold should be established for offering 'indirect' genetic testing to unaffected patients (no personal history of cancer) with a family history suggestive of a strong dominant genetic susceptibility to cancer, where there is no living affected relative available to test. Also, the cost-effectiveness of testing unaffected relatives of affected individuals will be assessed.

The evidence review identified four papers. All papers were deemed partially applicable to the guideline as the analyses were conducted in countries other than the UK or did not conform to one or more aspects of the NICE reference case. All papers were deemed to have very serious limitations. No reliable conclusions could be drawn from these papers. As decisions about who is eligible for genetic testing will significantly impact upon NHS resources and patient benefits, this topic was identified as a high economic priority by the GDG.

Aim

The aim of the economic evaluation was to assess at which carrier probability and which age genetic testing should offered to people with a family history of breast/ovarian cancer**.**

The following strategies were considered:

- Genetic testing
- No genetic testing (comparator)

Subgroup analyses were conducted for the following subgroups:

- People affected by breast/ovarian cancer (population 1)
- People unaffected by cancer with an affected relative available to test (population 2)
- People unaffected by cancer without an affected relative available to test (population 3)

Subgroup analyses were undertaken for the following age groups:

- 20-29 years
- 30-39 years
- 40-49 years
- 50-59 years
- 60-69 years
- >70 years

Subgroup analyses were conducted for the following carrier probabilities:

- 5% carrier probability
- 10% carrier probability
- 15% carrier probability
- 20% carrier probability
- 30% carrier probability
- 40% carrier probability

The economic model does not cover:

- Indirect effects of genetic testing on the relatives of the individual modelled as part of the populations described above
- Incidence of both breast and ovarian cancer within one year. This occurs in the very small proportion of patients.

Supplementary analysis

An important cost-effectiveness question raised by the GDG was the effect on family member(s) if an individual in groups 1 to 3 was tested. An economic appraisal of the potential benefits and risks in terms of the number of genetically at-risk relatives identified as a result of indirect testing was considered within a supplementary analysis

Inclusion of women and men

This topic was to be up-dated to include men, as this population had not been considered in CG14. However, the paucity of evidence on men was considered a potential challenge in developing the model. It was agreed by the GDG that men would be considered within the same population as women. However, a separate model has been built for men to allow specific analysis if and when appropriate data becomes available.

Model structure

A de novo economic model was built. The model for topic A was constructed in two stages:

Stage 1: A decision tree was used to reflect key events in the clinical pathway from diagnostic genetic testing through to risk-reducing surgery and disease progression (stage 2).

There are two arms in each tree: no genetic testing is offered (a) and genetic testing is offered (b). In populations 1 and 3, genetic testing is offered directly to the population member. The decision tree for population 2 includes an additional step in arm b, in which genetic testing is offered to the population member (unaffected individual) only if a positive result is obtained as a result of genetic testing in their relative, who is affected by cancer. It was assumed that the only risk-reducing surgery option available to men is mastectomy. Whilst rare, the GDG felt it should be reflected in the model.

Stage 2: A semi-Markov model was constructed to replicate the natural progression of disease following risk-reducing surgery decisions, made as a result of genetic testing or in its absence. A number of health states were included to model the incidence of new cancers, survival and death. Both cancer-related deaths and all-cause mortality were included. Transitions between health states were evaluated over annual cycles, over a modelled horizon of 50 years.

Separate models were developed for women and men. A UK NHS perspective has been adopted in the analysis. A life-time horizon has been taken.

Key model assumptions

A number of assumptions have been made in constructing the model based on GDG expert opinion:

- The base case analysis follows current standard practice and incorporates current recommendations for surveillance and treatment.
- A proportion of individuals may refuse diagnostic genetic testing if offered; these individuals follow the same pathway as those in the no testing arm.
- In individuals unaffected by cancer and with a living relative affected by cancer (Population 2), the assumption made is that the relative is willing to undergo diagnostic genetic testing. Any individual unaffected by cancer, with a living relative affected by cancer but whose relative was unwilling or unable to undergo genetic testing would fall into population 3.
- Regardless of whether a mutation is identified or not, a proportion of individuals may refuse or delay the uptake of risk-reducing surgery. The model simulates individuals delaying surgery by up to 5 years after genetic testing, if no new cancers have developed in that time.
- Affected individuals enter the model in an existing cancer health state.
- Unaffected individuals who are subsequently diagnosed and treated for cancer progress to an existing cancer health state on survival i.e. they become an affected individual.
- All individuals in an existing cancer health state are at increased risk of developing a new cancer
- Individuals with disease progression fully complete the treatment pathway, as per current standard practice, identified by the GDG.
- Menopausal status has consequences for the typical treatments given for breast cancer. As the mean age of menopause is approximately 51 years (Mishra and Kuh, 2012), it is assumed that all patients treated for breast cancer in age groups <50 years receive treatment typical of a premenopausal patient, while patients >50 years receive treatment typical of a postmenopausal patient.
- The surveillance of individuals with unknown *BRCA* status is assumed to consist of annual mammography for individuals with carrier probability up to 30% and annual MRI for individuals with carrier probability exceeding 30%.
- It is assumed that nobody has had risk-reducing surgery before genetic testing, or that the first uptake rate (year 1) of risk-reducing surgery includes those who have it before genetic testing.

Model Inputs

The cost-effectiveness analysis required relevant clinical evidence, health-related preferences (utilities), healthcare resource use and costs. A considerable challenge was presented when no relevant clinical evidence was identified for this topic. Therefore, structured searches had to be undertaken for all relevant parameters and, where published

evidence was limited, the expert opinion of the GDG was used to estimate relevant parameters. Men were not considered separately as a population due to lack of data.

Clinical data

Uptake and accuracy of genetic testing

The proportion of eligible and invited unaffected and affected individuals who choose not to take up genetic testing, were retrieved from published literature (Schwartz, *et al.,* 2004, Evans, *et al.,* 2009). Individuals who are not undergoing testing are automatically referred into the "no testing" branch of the decision tree in the model. The model accounts for the small potential for false positive and negative results by applying sensitivity (Smith, *et al.,* 2012) and specificity values to the process of genetic testing based on GDG expert opinion.

Uptake of risk-reducing surgery (RRS)

The model assumes that regardless of the outcome of testing, or whether testing is undertaken at all, some people will choose to undergo risk-reducing surgery i.e. mastectomy, bilateral salpingo-oophorectomy (BSO), or both. The model assumes that people who undergo risk-reducing surgery will do so within the first 5 years from offering/genetic testing with the majority taking up RRS within the first 2 years. Individuals below the age of 35 who have not completed family planning are assumed to postpone BSO for 5 years. In the model, this was applied as annual uptake with approximately 50% of people who decide to undergo RRS having surgery in year 1, 15% in year 2, 13% in year 3, 12% in year 4 and 10% in year 5 (these yearly proportions varied slightly based on the available data). The "no surgery" option for each year was calculated by adding all uptake values for all surgery options for each year and subtracting it from 100%.

Cancer type

The model assumes that people affected by cancer (population 1) had either breast or ovarian cancer and the proportions stated above were inflated to reflect this; i.e. 88.4% affected by breast cancer and 11.6% affected by ovarian cancer, based on current literature. Any uncertainty that might arise from this slight discrepancy was accounted for in the sensitivity analysis. Breast cancer was assumed to be node-positive in *BRCA2* and triple-negative in *BRCA1* carriers. Ovarian cancer includes fallopian and peritoneal cancer.

Cancer incidence

Cancer incidence data for people with a family history of breast cancer is relatively sparse and the available data is often based on small patient numbers (especially for *BRCA1*/2 mutation carriers). Based on GDG expert opinion, it was therefore decided to use incidence data produced by BOADICEA based on a 45-year old affected index individual (for the affected subpopulation) and her 20 year old unaffected daughter (for the unaffected subpopulation) from example families with a carrier probability of 5%, 10%, 15%, 20%, 30% and 40%, respectively. No new cancer incidence data was available for affected individuals aged 20 to 39 years as the calculations were based on a 45 year old affected woman. The baseline annual incidences (no RRS) as shown were then adjusted using risk reduction rates as published in the literature to account for the effects of the different risk-reducing surgery options on new cancer incidence.

Cancer-related mortality

Data on cancer-specific mortality have been taken from published literature and validated by the GDG.

Mortality (non-disease specific)

Interim life tables (2008-2010) were obtained from the Office for National Statistics[19] These allowed the identification of the life expectancy for each age group based on the general population.

Utility data

The model calculates the cost of genetic testing per quality adjusted life year (QALY) gained. This means that the analysis considers a change in quality of life as well as any additional life years which result from genetic testing. It was therefore necessary to estimate QALYs for various parameters such as cancer treatment and risk-reducing surgery. However, during the systematic review it became clear that there is a distinct lack of QALY data based on EQ-5D measures in the published literature which made it necessary for the GDG to make assumptions for some parameters based on their clinical expertise and experience. All utilities were discounted by 3.5%.

Baseline utility and effect of genetic testing

Baseline utilities were taken from literature and were based on UK data and EQ-5D wherever possible. The baseline utility of a person affected by breast cancer was determined to be 0.68 (Peasgood, *et al.,* 2010). Based on previous findings (Grann, *et al.,* 2011), genetic testing and especially a positive result can lead to anxiety in affected individuals. Comparing an average quality of life score of 0.90 for a person not suffering from breast cancer (Younis *et al.,* 2011) and the value for a person who is well but with a positive *BRCA* testing result of 0.895 reported by Grann, *et al.,* (2011), the utility decrement of genetic testing was set to 0.005. This decrement was only applied once at the time of testing.

Utility decrement associated with risk-reducing surgery

Previously, it has been suggested that risk-reducing surgery causes a person's utility score to drop temporarily due the effect of surgery on quality of life (Griffith, *et al.,* 2004, Peasgood *et al.,* 2010). The model therefore assumes a utility decrement of 0.03 for mastectomy (Peasgood, *et al.,* 2010) and 0.08 for oophorectomy (Griffith, *et al.,* 2004) in the year surgery is performed. The GDG advised that it would be very rare for both surgeries to be done at the same time, so an additive utility decrement of 0.11 was used for people who undergo both surgeries. No utility decrement is expected for subsequent years.

Utility during cancer treatment

Utility values for patients undergoing treatment for breast and ovarian cancer in year 1 were taken from literature (Havrilesky, *et al.,* 2009, Peasgood, *et al.,* 2010). Following GDG advice, a steady improvement in quality of life was then assumed for years 2 to 5. After 5 years, a utility score slightly higher than in year 5 was assumed.

Resource use and cost data

The costs considered in this analysis were those relevant to the UK NHS setting and included the cost of diagnostic genetic testing, treatment (including expected in-patient and out-patient costs) and surveillance. Unit costs were based on the BNF, NHS Reference Costs (2011) and Unit Costs of Health and Social Care (Curtis, 2011).

[19] Office for National Statistics (http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Interim+Life+Tables).

All costs were discounted by 3.5%.

Sensitivity analysis

Three different sensitivity analyses were conducted to test the robustness of the results of each economic model. One way sensitivity analysis was undertaken to test the robustness of the model to changes in key parameters. Probabilistic sensitivity analysis was performed to test the robustness of the model against a range of variations in the model parameters.

A supplementary analysis was conducted to give an indication of the potential costs and benefits for family members of individuals identified as *BRCA*-positive. In order to conduct analysis of the cost-effectiveness of genetic testing for a family at a certain carrier probability, hypothetical families were drawn up from BOADICEA for each carrier probability threshold of interest .The model was individually set up for each family member (carrier probability of the family, individual age and affected/unaffected by cancer) and the model was run with a cohort size of 1. This analysis therefore takes into account costs and benefits for the index individual and adds any costs and benefits arising from testing of family members of a positive individual (e.g. cost of additional genetic testing, cost of screening, improved survival through early detection etc.). These additional costs and benefits for family members tested after the index individual tested positive were considered knock-on effects of genetic testing of an index individual.

Results– base case

Women affected by breast cancer (population 1)

Age groups: 20-29 years and 30-39 years

The incidence of new breast cancer data generated by BOADICEA was based on an affected woman of age 45 years. For this reason, no incidence data was available for affected individuals below the age of 40 years.

Age group: 40-49 years

Table 6.2 presents the full range of ICERs calculated for various screening strategies in individuals aged 40-49 years.

Table 6.2: Summary of ICERs of genetic testing in individuals aged 40 to 49 years *(population 1)*

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	£19,218	Genetic testing cost-effective at £20,000 CE threshold
10%	£18,114	Genetic testing cost-effective at £20,000 CE threshold
15%	£17,627	Genetic testing cost-effective at £20,000 CE threshold
20%	£17,697	Genetic testing cost-effective at £20,000 CE threshold
30%	£17,650	Genetic testing cost-effective at £20,000 CE threshold
40%	£17,591	Genetic testing cost-effective at £20,000 CE threshold

The results identified that in women aged 40-49 years affected by breast cancer, for each risk threshold, genetic testing was cost-effective at a WTP of £20,000.

Age group: 50-59 years

Table 6.3 presents the full range of ICERs calculated for various screening strategies in individuals aged 50-59 years.

Table 6.3: Summary of ICERs of genetic testing in individuals aged 50 to 59 years (population 1)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	£26,127	Genetic testing cost-effective at £30,000 CE threshold
10%	£25,729	Genetic testing cost-effective at £30,000 CE threshold
15%	£25,419	Genetic testing cost-effective at £30,000 CE threshold
20%	£25,760	Genetic testing cost-effective at £30,000 CE threshold
30%	£26,237	Genetic testing cost-effective at £30,000 CE threshold
40%	£26,915	Genetic testing cost-effective at £30,000 CE threshold

The results identified that in women aged 50-59 years affected by breast cancer, for each risk threshold, genetic testing was not cost-effective at a WTP of £20,000 but would be considered cost-effective with a WTP of £30,000.

Age group: 60-69 years

Table 6.4 presents the full range of ICERs calculated for various screening strategies in individuals aged 60-69 years.

Table 6.4: Summary of ICERs of genetic testing in individuals aged 60 to 69 years (population 1)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	£42,178	Genetic testing not cost-effective
10%	£42,534	Genetic testing not cost-effective
15%	£42,207	Genetic testing not cost-effective
20%	£42,622	Genetic testing not cost-effective
30%	£43,410	Genetic testing not cost-effective
40%	£44,744	Genetic testing not cost-effective

The results identified that in women aged 60-69 years affected by breast cancer, for each risk threshold, genetic testing was not cost-effective at a WTP of £20,000 or at a WTP threshold of £30,000.

Age group: 70+ years

Table 6.5 presents the full range of ICERs calculated for various screening strategies in individuals aged >70 years.

Table 6.5: Summary of ICERs of genetic testing in individuals aged 70+ years (population 1)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	£83,698	Genetic testing not cost-effective
10%	£84,410	Genetic testing not cost-effective
15%	£83,789	Genetic testing not cost-effective
20%	£84,206	Genetic testing not cost-effective
30%	£85,215	Genetic testing not cost-effective
40%	£87,153	Genetic testing not cost-effective

The results identified that in women aged 70 years and above affected by breast cancer, for each risk threshold, genetic testing was not cost-effective at a WTP of £20,000 or at a WTP threshold of £30,000.

Women unaffected by cancer (with no personal history) – with a living relative to test (population 2)

Age group: 20-29 years

Table 6.6 presents the full range of ICERs calculated for various screening strategies in individuals aged 20-29 years.

Table 6.6: Summary of ICERs of genetic testing in individuals aged 20 to 29 years (population 2)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	£20,348	Genetic testing cost-effective at £30,000 CE threshold
10%	£16,741	Genetic testing cost-effective at £20,000 CE threshold
15%	£14,406	Genetic testing cost-effective at £20,000 CE threshold
20%	£12,870	Genetic testing cost-effective at £20,000 CE threshold
30%	£6,168	Genetic testing cost-effective at £20,000 CE threshold
40%	£5,083	Genetic testing cost-effective at £20,000 CE threshold

The results identified that in individuals aged 20-29 years with a 5% carrier probability, genetic testing was just above a WTP threshold of £20,000 but well within a WTP threshold of £30,000. Genetic testing in higher risk populations was cost-effective at a WTP of £20,000.

Age group: 30-39 years

Table 6.7 presents the full range of ICERs calculated for various screening strategies in individuals aged 30-39 years.

Table 6.7: Summary of ICERs of genetic testing in individuals aged 30 to 39 years (population 2)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	£13,402	Genetic testing cost-effective at £20,000 CE threshold
10%	£11,571	Genetic testing cost-effective at £20,000 CE threshold
15%	£10,208	Genetic testing cost-effective at £20,000 CE threshold
20%	£9,327	Genetic testing cost-effective at £20,000 CE threshold
30%	£4,665	Genetic testing cost-effective at £20,000 CE threshold
40%	£3,911	Genetic testing cost-effective at £20,000 CE threshold

The results identified that all individuals aged 30-39 years with a 5% or greater carrier probability, genetic testing was cost-effective.

40-49 years

Table 6.8 presents the full range of ICERs calculated for various screening strategies in individuals aged 40-49 years.

Table 6.8: Summary of ICERs of genetic testing in individuals aged 40 to 49 years (population 2)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	£13,625	Genetic testing cost-effective at £20,000 CE threshold
10%	£12,108	Genetic testing cost-effective at £20,000 CE threshold
15%	£10,838	Genetic testing cost-effective at £20,000 CE threshold
20%	£9,996	Genetic testing cost-effective at £20,000 CE threshold
30%	£5,493	Genetic testing cost-effective at £20,000 CE threshold
40%	£4,730	Genetic testing cost-effective at £20,000 CE threshold

The results identified that in individuals aged 40-49 years genetic testing was cost-effective

50-59 years

Table 6.9 presents the full range of ICERs calculated for various screening strategies in individuals aged 50-59 years.

Table 6.9: Summary of ICERs of genetic testing in individuals aged 50 to 59 years (population 2)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	£20,821	Genetic testing cost-effective at £30,000 CE threshold
10%	£18,954	Genetic testing cost-effective at £20,000 CE threshold
15%	£17,295	Genetic testing cost-effective at £20,000 CE threshold
20%	£16,097	Genetic testing cost-effective at £20,000 CE threshold
30%	£10,176	Genetic testing cost-effective at £20,000 CE threshold
40%	£9,070	Genetic testing cost-effective at £20,000 CE threshold

The results identified that in individuals aged 50-59 years with a 5% risk, genetic testing was just above a WTP threshold of £20,000 but well within a WTP threshold of £30,000. All higher risk populations were cost-effective at a WTP of £20,000.

Age group: 60-69 years

Table 6.10 presents the full range of ICERs calculated for various screening strategies in individuals aged 60-69 years.

Table 6.10: Summary of ICERs of genetic testing in individuals aged 60 to 69 years (population 2)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	£39,823	Genetic testing not cost-effective
10%	£36,647	Genetic testing not cost-effective
15%	£33,882	Genetic testing not cost-effective
20%	£31,590	Genetic testing not cost-effective
30%	£22,231	Genetic testing cost-effective at £30,000 CE threshold
40%	£20,056	Genetic testing cost-effective at £30,000 CE threshold

The results identified that in individuals aged 60-69 years and above affected by breast cancer, with a carrier of risk of <30%, genetic testing was not cost-effective at a WTP of £20,000 or at a WTP threshold of £30,000. Genetic testing fell within a WTP threshold of £30,000 for individuals with a >30% risk.

Age group: 70+ years

Table 6.11 presents the full range of ICERs calculated for various screening strategies in individuals aged >70 years.

Table 6.11: Summary of ICERs of genetic testing in individuals aged 70+ years (population 2)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	£113,629	Genetic testing not cost-effective
10%	£102,968	Genetic testing not cost-effective
15%	£94,395	Genetic testing not cost-effective
20%	£87,029	Genetic testing not cost-effective
30%	£65,682	Genetic testing not cost-effective
40%	£58,390	Genetic testing not cost-effective

The results identified that in women aged 70 years and above affected by breast cancer, for each carrier probability, genetic testing was not cost-effective at a WTP of £20,000 or at a WTP threshold of £30,000.

Women unaffected by cancer (with no personal history) – without a living relative to test (population 3)

Age group: 20-29 years

Table 6.12 presents the full range of ICERs calculated for various screening strategies in individuals aged 20-29 years.

Table 6.12: Summary of ICERs of genetic testing in individuals aged 20 to 29 years (population 3)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	dominating	Genetic testing cost-effective at £20,000 CE threshold
10%	dominating	Genetic testing cost-effective at £20,000 CE threshold
15%	dominating	Genetic testing cost-effective at £20,000 CE threshold
20%	dominating	Genetic testing cost-effective at £20,000 CE threshold
30%	dominating	Genetic testing cost-effective at £20,000 CE threshold
40%	dominating	Genetic testing cost-effective at £20,000 CE threshold

Age group: 30-39 years

Table 6.13 presents the full range of ICERs calculated for various screening strategies in individuals aged 30-39 years.

Table 6.13: **Summary of ICERs of genetic testing in individuals aged 30 to 39 years (population 3)**

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	dominating	Genetic testing cost-effective at £20,000 CE threshold
10%	dominating	Genetic testing cost-effective at £20,000 CE threshold
15%	dominating	Genetic testing cost-effective at £20,000 CE threshold
20%	dominating	Genetic testing cost-effective at £20,000 CE threshold
30%	dominating	Genetic testing cost-effective at £20,000 CE threshold
40%	dominating	Genetic testing cost-effective at £20,000 CE threshold

Age group: 40-49 years

Table 6.14 presents the full range of ICERs calculated for various screening strategies in individuals aged 40-49 years.

Table 6.14: Summary of ICERs of genetic testing in individuals aged 40 to 49 years (population 3)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	dominating	Genetic testing cost-effective at £20,000 CE threshold
10%	dominating	Genetic testing cost-effective at £20,000 CE threshold
15%	dominating	Genetic testing cost-effective at £20,000 CE threshold
20%	dominating	Genetic testing cost-effective at £20,000 CE threshold
30%	dominating	Genetic testing cost-effective at £20,000 CE threshold
40%	dominating	Genetic testing cost-effective at £20,000 CE threshold

Age group: 50-59 years

Table 6.15 presents the full range of ICERs calculated for various screening strategies in individuals aged 50-59 years.

Table 6.15: Summary of ICERs of genetic testing in individuals aged 50 to 59 years (population 3)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	dominating	Genetic testing cost-effective at £20,000 CE threshold
10%	dominating	Genetic testing cost-effective at £20,000 CE threshold
15%	£636	Genetic testing cost-effective at £20,000 CE threshold
20%	£1,467	Genetic testing cost-effective at £20,000 CE threshold
30%	dominating	Genetic testing cost-effective at £20,000 CE threshold
40%	dominating	Genetic testing cost-effective at £20,000 CE threshold

Age group: 60-69 years

Table 6.16 presents the full range of ICERs calculated for various screening strategies in individuals aged 60-69 years.

Table 6.16: Summary of ICERs of genetic testing in individuals aged 60 to 69 years (population 3)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	£3,491	Genetic testing cost-effective at £20,000 CE threshold
10%	£5,030	Genetic testing cost-effective at £20,000 CE threshold
15%	£6,329	Genetic testing cost-effective at £20,000 CE threshold
20%	£7,555	Genetic testing cost-effective at £20,000 CE threshold
30%	dominating	Genetic testing cost-effective at £20,000 CE threshold
40%	dominating	Genetic testing cost-effective at £20,000 CE threshold

Age group: 70+ years

Table 6.17 presents the full range of ICERs calculated for various screening strategies in individuals aged >70 years.

Table 6.17: Summary of ICERs of genetic testing in individuals aged 70+ years (population 3)

Percentage carrier probability	ICER (£/QALY)	Interpretation of results
5%	£30,015	Genetic testing not cost-effective
10%	£31,913	Genetic testing not cost-effective
15%	£33,600	Genetic testing not cost-effective
20%	£35,057	Genetic testing not cost-effective
30%	£9,616	Genetic testing cost-effective at £20,000 CE threshold
40%	£15,534	Genetic testing cost-effective at £20,000 CE threshold

The ICERs generated by the model exhibit a drop at 30% carrier probability as a result of different costs applied to healthy individuals in different population subgroups within the model. In order to derive costs for individuals in the healthy state, the GDG specified different screening strategies according to *BRCA* status. Women known to be *BRCA* positive were assumed to receive MRI screening, while those known to be *BRCA* negative received no screening. Women with unknown *BRCA* status received screening dependent on their carrier probability; with mammography used at less than 30% carrier probability and MRI at 30% or more.

Since MRI is a more expensive screening strategy than mammography, the cost of managing healthy women with unknown *BRCA* status is more costly at 30% carrier probability. By identifying *BRCA* negative individuals through genetic testing, there are greater potential savings to be made (while women are still healthy) above 30% carrier probability (avoided MRI screening), than below (avoided mammography screening). However, as carrier probability increases genetic testing identifies fewer individuals as being *BRCA* negative and so fewer savings can be made by avoiding screening costs (either mammography or MRI).

One-way sensitivity analysis

Due to the very high number of subgroups that were analysed for this topic, one-way sensitivity analysis was conducted in spot checks for several age groups and carrier probabilities rather than as a complete analysis for all subgroups. All spot checks demonstrated that the results of the analyses are reasonably robust to changes of single parameters.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was undertaken for the age groups 40-69 years as cost-effectiveness of these were most likely to change when uncertainty of parameters was accounted for. However, all results were found to be robust.

Supplementary analysis

Two sets of analyses were conducted in order to investigate the cost-effectiveness of family testing:

- Male relatives excluded
- Male relatives run through the model for women

Genetic testing for the family members of an index individual found to be *BRCA*-positive was cost-effective for all scenarios tested. Table 6.18 summarises the incremental cost and benefits (QALYs) for families with different carrier probability.

Table 6.18: Incremental cost and QALYs generated by genetic testing of family members

Percentage carrier probability	1: Men excluded		2: Men included	
	Incremental Cost	Incremental Benefit	Incremental Cost	Incremental Benefit
5%	£691	0.237	£622	0.321
10%	-£695	0.170	-£657	0.260
15%	£2,109	0.288	£2,250	0.384
20%	£2,524	0.306	£2,776	0.406
30%	-£884	0.355	-£1,619	0.468
40%	£3,083	0.373	£2,648	0.496

When combined with the base case results, cost-effectiveness results remain cost-effective for all results that were cost-effective in the base case and are improved for some patient subgroups (tables 6.19 to 6.21).

Table 6.19: Improved cost-effectiveness (marked in bold) for base case individuals aged 50-59 years when family testing knock on effects are considered

Percentage carrier probability	Cost-effectiveness of genetic testing (50-59 years)		
	Population 1	Population 2	Population 3
5%	**(£19,204 - £20,822)**	**Cost-effective**	Cost-effective
10%	**Cost-effective**	Cost-effective	Cost-effective
15%	**Cost-effective**	Cost-effective	Cost-effective
20%	**Cost-effective**	Cost-effective	Cost-effective
30%	**Cost-effective**	Cost-effective	Cost-effective
40%	**Cost-effective**	Cost-effective	Cost-effective

Note: the same family profile applied regardless of age of index individual

Table 6.20: Improved cost-effectiveness (marked in bold) for base case individuals aged 60-69 years when family testing knock on effects are considered

Percentage carrier probability	Cost-effectiveness of genetic testing (60-69 years)		
	Population 1	Population 2	Population 3
5%	Not cost-effective	Not cost-effective	Cost-effective
10%	Not cost-effective	Not cost-effective	Cost-effective
15%	**(£18,043 - £21,341)**	**(£17,513 - £20,252)**	Cost-effective
20%	**Cost-effective**	**Cost-effective**	Cost-effective
30%	**Cost-effective**	**Cost-effective**	Cost-effective
40%	**Cost-effective**	**Cost-effective**	Cost-effective

Note: the same family profile applied regardless of age of index individual

Table 6.21: Improved cost-effectiveness (marked in bold) for base case individuals aged >70 years when family testing knock on effects are considered

Percentage carrier probability	Cost-effectiveness of genetic testing (>70 years)		
	Population 1	Population 2	Population 3
5%	Not cost-effective	Not cost-effective	**Cost-effective**
10%	Not cost-effective	Not cost-effective	**Cost-effective**
15%	Not cost-effective	Not cost-effective	**Cost-effective**
20%	**(£19,400 - £23,808)**	Not cost-effective	**Cost-effective**
30%	**Cost-effective**	**Cost-effective**	Cost-effective
40%	**Cost-effective**	**Cost-effective**	Cost-effective

Note: the same family profile applied regardless of age of index individual

Summary of results

The aim of this economic analysis was to assess the cost-effectiveness of genetic testing compared to no genetic testing in different patient populations, age groups and carrier probability groups and to estimate the effect of relative cascade testing on cost-effectiveness of genetic testing.

Affected individuals (population 1)

- Genetic testing is expected to be cost-effective for all carrier probability groups between the age of 40 and 49 years if only the impact on the index individual is considered in the analysis
- Incidence of new breast cancer was based on an affected individual aged 45 years. For this reason no analyses were conducted for affected individuals below the age of 40. However, since incidence of new breast cancer increases as the age of diagnosis of primary cancer decreases (Malone, *et al.,* 2010), it is expected that genetic testing will be cost-effective for all risk groups between the ages 20 to 39 years.
- Genetic testing of the affected index individual only is not expected to be cost-effective for individuals aged 50 years and over.

Affected individuals (population 1) have a higher incidence of developing new breast and ovarian cancer compared to unaffected individuals. All individuals in this population will receive cancer treatment at least once during their lifetime. Risk-reducing surgery and genetic testing uptake are also higher in affected individuals. Furthermore, mortality is higher in the affected population and they are more likely to die from cancer than from other causes when compared to the unaffected population. Thus, the overall costs of the affected population are considerably higher and their quality of life is lower than the unaffected populations. Consequently, genetic testing provides fewer cost savings and quality of life benefits later in life for the affected population and is not particularly cost-effective if only the cost and benefits of the affected index individual are included in the analysis.

Unaffected individuals with an affected relative available to be tested (population 2)

- Genetic testing is expected to be cost-effective for 20-29 year old unaffected individuals whose affected relative has been tested first from 10% carrier probability upwards.
- Genetic testing is expected to be cost-effective for all carrier probability thresholds tested for unaffected individuals between the ages of 30 and 49 years.

- Genetic testing is expected to be cost-effective for 50-59 year old unaffected individuals whose affected relative has been tested first from 10% carrier probability upwards.
- Genetic testing for this population is not expected to be cost-effective at a £ 20,000/QALY threshold for any carrier probability from 60 years onwards.

Analyses suggest that genetic testing will be cost-effective for most age and carrier probability groups when the focus of analysis is the impact of testing on an unaffected individual, who undergoes genetic testing based on the prior result of testing in an affected relative. These results suggest that in many scenarios the cost of testing an affected index individual is sufficiently offset by the costs and benefits of one unaffected relative (population 2 member) to be considered cost-effective.

An unaffected individual is expected to receive the optimum benefits of genetic testing such as reduced incidence of primary breast and ovarian cancers and subsequent morbidity and mortality in individuals found to be *BRCA* positive and who choose to undergo risk-reducing surgery as a result, or the reduction of unnecessary risk-reducing surgery in individuals found to be *BRCA* negative. Furthermore, cost savings may be achieved as a result of genetic testing for the same reasons, and also as a result of reduced surveillance in those individuals found to be *BRCA* negative.

Unaffected individuals without an affected relative available to be tested (population 3)

- Genetic testing is expected to dominate for all carrier probabilities for age groups 20 to 49 years. That is, it is more effective and less expensive than no testing.
- Genetic testing is expected to be highly cost-effective for all carrier probabilities for age groups 50 to 69 years.
- Genetic testing is expected to be cost-effective for unaffected individuals over 70 years with at least a 30% carrier probability.

The results of population 3 (unaffected individuals who have no affected relative available to test) are highly cost-effective if only the costs and benefits of this single individual are considered. Unaffected individuals in population 3 accumulate all benefits and cost savings described for population 2 however the total cost of testing is lower in this scenario. With no unaffected relative available to test the unaffected individual is the index individual and only one test is conducted to determine whether this individual carries a mutation, while in population 2 one index test was conducted and a possible further test of the unaffected individual. Furthermore, all unaffected individuals in this scenario are offered testing leading to higher potential cost savings in surveillance for those identified as *BRCA* negative.

Supplementary analysis

- Cost-effectiveness is expected to be significantly improved if cascade testing of relatives is taken into account in addition to testing the single individuals of populations 1 to 3.
- Analysis of hypothetical family profiles suggests that at 10% carrier probability genetic testing will be cost-effective in all individuals aged 20-59 years and in unaffected individuals with no affected relative to test aged at least 60 years.
- The family profiles tested did not show significantly improved cost-effectiveness of genetic testing in several family members with increasing carrier probability. This may be due to the following reasons:

- Lower risk families have a greater proportion of family members with no personal history of cancer, for whom genetic testing is expected to be more cost-effective than affected individuals.
- Genetic testing in low risk families identifies a higher proportion of *BRCA*-negative individuals, for whom greater cost savings may be generated while they remain in the "no cancer" state due to reduced screening.

- Cost-effectiveness (especially of older age groups) is significantly improved if cascade testing of relatives is taken into account in addition to testing the single individuals of populations 1 to 3.

Recommendations

- For a person with no personal history of breast cancer, offer genetic testing in tertiary care to a family member with breast or ovarian cancer if their combined *BRCA1* and *BRCA2* mutation carrier probability is 10% or more (or they have a Manchester score of 15 or more). **[new 2013]**
- For a person with no personal history of breast cancer, consider genetic testing in tertiary care for a family member with breast cancer or ovarian cancer if their combined *BRCA1* and *BRCA2* mutation carrier probability is between 5% and 10%. **[new 2013]**
- Offer genetic testing in tertiary care to a person with no personal history of breast or ovarian cancer if their combined *BRCA1* and *BRCA2* mutation carrier probability is 10% or more, when they have a first-degree affected relative with a carrier probability of 20% in the family but is unavailable for testing (or a Manchester score of 17 or more). **[new 2013]**
- Consider genetic testing in tertiary care for a person with no personal history of breast or ovarian cancer if their combined *BRCA1* and *BRCA2* mutation carrier probability is between 5% and 10% when they have a first-degree affected relative with a carrier probability of 10 - 20% in the family but is unavailable for testing (or a Manchester score of 14-16). **[new 2013]**
- For a person with a personal history of breast and/or ovarian cancer offer genetic testing in tertiary care if their combined *BRCA1* and *BRCA2* mutation carrier probability is 10% or more (or a Manchester score of 15 or more). **[new 2013]**
- For a person with a personal history of breast and/or ovarian cancer, consider genetic testing in tertiary care if their combined *BRCA1* and *BRCA2* mutation carrier probability is between 5% and 10%. **[new 2013]**
- Clinical genetics laboratories should record gene variants of uncertain significance, periodically review for evidence of causality and ensure that families are contacted as appropriate. **[new 2013]**

Linking Evidence to Recommendations

The aim of this topic was to investigate the carrier probability at which genetic testing should be offered to:

- individuals with no personal history of breast or ovarian cancer with a living affected family member available to test
- individuals with no personal history of breast or ovarian cancer and without a living affected family member available to test
- individuals with a personal history of breast or ovarian cancer.

The GDG acknowledged that there was no clinical evidence comparing different carrier probability thresholds for genetic testing for any of these population groups. However the

GDG noted that a health economic analysis had been undertaken and considered the estimated cost-effectiveness results of genetic testing for individuals and also their family members.

The GDG noted that for individuals with no personal history but with a living affected family member available to test, the health economic analysis indicated that genetic testing would be cost-effective at both 5% and 10% carrier probability up to the age of 60. The GDG acknowledged that the results also indicated that genetic testing was only likely to be cost-effective at a £20,000/QALY threshold for individuals 60 years and over at higher carrier probabilities. Although the GDG acknowledged the vast majority if requests for genetic tests are from individuals under the age of 60, they did not want to exclude those over 60 from being offered testing. Therefore to avoid any inequity the GDG decided not to recommend an upper age limit for genetic testing.

The GDG noted that for individuals with no personal history and without a living affected family member available to test, the health economic analysis indicated that genetic testing would be cost effective at both 5% and 10% carrier probabilities across all age groups.

The GDG noted that for individuals with a personal history of breast or ovarian cancer, the health economic analysis indicated that genetic testing would be cost effective at both 5% and 10% carrier probabilities up to the age of 60. The GDG acknowledged that no incidence data was available for individuals under 40. However, since genetic testing was cost effective for the 40-49 age group and incidence of new breast cancer has been shown to be higher the younger the affected person at first diagnosis, the GDG agreed it could be assumed that genetic testing would be cost-effective for the younger age groups.

The GDG also acknowledged that the results of the analysis, for individuals with a personal history, indicated that genetic testing was only likely to be cost-effective at a £20,000/QALY threshold for individuals 60 years and over at higher carrier probabilities (>10%). Although the GDG acknowledged the vast majority of requests for genetic tests are from individuals under the age of 60, they did not want to exclude those over 60 from being offered testing. Therefore to avoid any inequity the GDG decided not to recommend an upper age limit for genetic testing.

The GDG agreed that the results of the health economic analysis supported genetic testing at 10% carrier probability. The GDG noted that the potential benefits of recommending this included reduced morbidity and mortality, reduced variation in practice, increased patient choice, improvement in informed decision making and a reduction in unnecessary surgery/treatment. Potential harms resulting from the recommendations identified by the GDG included more families and individuals experiencing uncertainty/anxiety (due to increased number of variants of unknown significance) and the potential increased waiting times for testing. However the GDG agreed that the benefits outweighed the harms.

The GDG also discussed whether it was appropriate to recommend a lower carrier probability for genetic testing, given that the results of the health economic analysis had indicated a 5% probability would be cost-effective for some age groups. The GDG noted that setting the carrier probability for genetic testing to 10% would prevent individuals with a carrier probability slightly lower than 10% from accessing genetic testing. However the GDG agreed that lowering the threshold to 5% for everyone would increase the number of patients eligible for genetic testing and potentially overload the existing service. Therefore the GDG decided to recommend that an individual with a carrier probability of 5% - 10% be considered for genetic testing.

The GDG also considered that when recommending genetic testing at the 5-10% carrier probability there is a high possibility of identifying a variant of unknown significance rather than a known causative mutation. Explaining a variant of unknown significance is difficult and can leave the tested person with uncertainty about the cause of their cancer or their future cancer risk or the risk to other family members. The GDG therefore agreed to recommend that clinical genetics laboratories should record gene variants of uncertain significance, periodically review for evidence of causality and ensure that families are contacted as appropriate.

Due to the paucity of data relevant to men at familial risk of breast cancer, no modelling could be conducted specific to men. However the GDG agreed that the recommendations made were applicable to both women and men.

6.4 Genetic testing for *BRCA1 BRCA2* and *TP53* within 4 weeks of diagnosis of breast cancer.

The object of this topic was to determine whether different breast cancer treatment and surveillance options might achieve better long-term outcomes (reduced morbidity/mortality) for *BRCA1/BRCA2/TP53* carriers if a gene alteration is identified soon after diagnosis.

For patients with a newly diagnosed breast cancer there are a number of treatment options available to them including targeted treatments (chemotherapy, radiotherapy, and surgery), risk-reducing surgery (mastectomy/bilateral salpingo-oophorectomy) or a combination of these.

Standard breast cancer treatments are aimed at removing the original cancer and mitigating the risk of any future relapse. Treatment is based largely on the risks and benefits of the differing options according to the likelihood of relapse (stage and biology) and the likely efficacy of any given treatment option (tumour grade, immunohistochemistry).

In *BRCA* gene carriers decisions are made in the same way as for sporadic breast cancers at present and do not usually take into account the *BRCA* mutation status, even when known. The exception may be for *BRCA* carriers who already know their genetic status and have already considered risk-reducing surgical options in the past and who may then express a preference for their surgical management.

It is unclear if there is a benefit or not of identifying *BRCA* gene carriers in order to determine best cancer treatment. If a benefit was confirmed then there would be grounds for the pathway to genetic testing being accelerated.

In considering this topic it is important to note that both medical interventions and particularly irreversible surgical risk-reducing interventions (mastectomy and bilateral salpingo-oophorectomy) are usually made after a considerable period of information exchange and reflection and may not be ideally made as urgent decisions at a time when decisions about cancer treatment are also being made.

Clinical Question: Does knowing the mutation status of a patient at or soon after cancer diagnosis affect the different cancer treatment options and/or does it usefully inform immediate decisions about risk-reducing options?

Clinical evidence (2013) (see also full evidence review)

Evidence statements

Treatment Decision

Very low quality evidence suggests that genetic test results influence treatment decisions (table 6.22). A prospective case series (Scheuer, *et al.,* 2002) reported changes in treatment decision based on genetic test results for both breast and ovarian surgeries. Another retrospective case series of low quality (Schwartz, *et al.,* 2004) reported that patients found to carry a *BRCA1*/2 mutation were significantly more likely to undergo bilateral mastectomy as compared with patients with uninformative results or women who opted not to be tested (48% versus 24% versus 4%; p<0.001).

Response to chemotherapy

Very low quality evidence suggests that response to chemotherapy may differ in *BRCA1*/2 carriers and non carriers (Forquet, *et al.,* 2009; (table 6.22). *BRCA1*/2 mutation was significantly associated with complete response to chemotherapy (RR=3.61; 95% CI 1.19-10.9).

Response to radiotherapy

There was insufficient evidence to say whether response to radiotherapy differs in *BRCA1*/2 carriers and non carriers. From one retrospective case series of very low quality (Forquet, *et al.,* 2009; (table 6.22) in 6 *BRCA1*/2 carriers, 1 had a complete response and 5 had a major response compared with 3 complete responses, 4 major responses and 6 minor/no response in the non-mutated tumours .

Relative effectiveness of mastectomy and breast conserving therapy

There was insufficient evidence to say whether knowledge of mutation status before making decisions about surgery influences outcome. Very low quality evidence from an observational study (Pierce, *et al.,* 2010; table 6.22) suggests local failure is significantly more likely following breast conserving therapy (BCT) than after mastectomy in patients with *BRCA1*/2 mutation. Median time to failure was 7.8 years for BCT patients and 9 years for mastectomy patients. But the clinical significance of this is unclear and there was no significant difference between the overall survival of the two treatment groups.

Risk-reducing Salpingo-Oophorectomy versus Surveillance

Very low quality evidence suggests that salpingo-oophorectomy lowers the incidence of gynaecological cancer compared to surveillance in women with *BRCA1*/2 mutation (Kauff, *et al.,* 2008; table 6.22). Following salpingo-oophorectomy the incidence rate was 3/509 compared with 12/283 in the surveillance group (HR=0.12, 95% CI, 0.03-0.41).

Very low quality evidence suggests that salpingo-oophorectomy lowers the incidence of breast cancer when compared to surveillance in women with *BRCA1*/2 mutation (Kauff, *et al.,* 2008; table 6.22). Following salpingo-oophorectomy the incidence rate was 19/303 compared with 28/294 in the surveillance group (HR=0.53, 95% CI, 0.29-0.96).

Table 6.22: - GRADE Profile: Does knowing the mutation status of a patient at or soon after cancer diagnosis affect the different cancer treatment options , treatment outcomes, incidence of future breast or ovarian cancer and/or does it affect the treatment decision?

Quality assessment							Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	
Rate of risk-reducing mastectomy							
Evans *et al.,* (2005); Kiely *et al.,* (2010); Schwartz *et al.,* (2004)							
3[1]	observational studies	serious[2]	very serious[3]	no serious indirectness[4]	serious[5]	none	VERY LOW
Rate of Risk-Reducing Salpingo Oophorectomy							
Scheuer *et al.,* (2002)							
1[6]	observational studies	serious[7]	no serious inconsistency[8]	serious[9]	serious[10]	none	VERY LOW
Change in treatment decision							
Scheuer *et al.,* (2002)							
1[6]	observational studies	serious[8,11]	no serious inconsistency[8]	serious[12]	serious[13]	none	VERY LOW
Clinical Response to Chemotherapy or Radiotherapy							
Forquet *et al.,* (2009)							
1[14]	observational studies	serious[15]	no serious inconsistency[8]	no serious indirectness	serious[16]	none	VERY LOW
Incidence of gynaecological cancer							
Kauff *et al.,* (2008)							
1[22]	observational studies	serious[17]	no serious inconsistency[8]	serious[18]	serious[19]	none	VERY LOW
Incidence of breast cancer							
Kauff *et al.,* (2008)							
1[22]	observational studies	serious[17]	no serious inconsistency[8]	serious[18]	serious[20]	none	VERY LOW
Cancer Recurrence							
Pierce *et al.,* (2010)							
1[23]	observational studies	serious[17]	no serious inconsistency[8]	serious[18]	serious[21]	none	VERY LOW

[1] Evans *et al.,* (2005), Kiely *et al.,* (2010) and Schwartz *et al.,* (2004)
[2] Non of the included studies were randomised trials, all were retrospective case series studies with no blinding apparent and no indication as to whether all available eligible patients were included in each study.
[3] All three studies reporting on the rates of mastectomy were reporting on different elements of the same outcome. Mastectomy outcomes included bilateral risk-reducing mastectomy and unilateral mastectomy. Populations included in each study varied slightly in relation to timing of genetic testing and knowledge of test results and therefore could not be compared and pooled.
[4] Overall the populations included in each of the three studies were considered to be directly relevant to the topic in question. In particular, Evans *et al.,* (2005) included only patients with a family history and recent diagnosis of breast cancer and also identified decisions made with and without knowledge of genetic test result. In addition, this study represents the only study carried out in a UK population.
[5] Two of the included studies (Evans *et al.*,, 2005 and Schwartz *et al.*,, 2004) included populations of only 70 patients and 194 patients respectively. Kiely *et al.,* (2010) included a population of 1018 and would therefore be considered likely to provide the most precise results.
[6] Scheuer *et al.,* (2002)
[7] The only study reporting on rates of risk-reducing salpingo-oophorectomy as a primary outcome was not a randomised trial.
[8] There was only a single study available to address this outcome in a relevant population therefore no comment can be made on the consistency of the result.
[9] The study included only patients with known *BRCA* mutations, comparing *BRCA1* mutation carriers with *BRCA2* mutation carriers. The *BRCA* mutation carrier population and their outcomes following treatment are of relevance to this topic however the comparison of interest was to patients who do not have a knowledge of the *BRCA* status. This study should be considered indirect for two reasons: it does not identify whether the *BRCA1*/2 patients included in this study were aware of their mutation status prior to treatment and it does not include a comparison of patients who were and were not aware of mutation status prior to treatment.
[10] This was a small observational study with a total population of 251 patients.
[11] There was only a single, retrospective case series available to address this outcome
[12]The population for this study included patients who were unaware of their mutation status at time of diagnosis and who underwent treatment prior to receiving test results, some of whom then underwent further treatment following receipt of genetic test results. There is no comparison with patients receiving definitive treatment only after receiving genetic test results.
[13] Small study with only 251 patients included
[14] Forquet *et al.,* (2009)
[15] The study was a retrospective case series which examined clinical response to treatment with chemotherapy and radiotherapy without any comparison to each other or to no treatment. The preferred study type for such a comparison would be a randomised controlled trial
[16] This was a small study with only 90 patients included
[17] Not a randomised Controlled Trial
[18] Only women known to be *BRCA1*/*BRCA2* carriers were included in the study and no information provided on whether they had knowledge of mutation status or not prior to surgery
[19] No explanation was provided
[20] The number of events recorded during the study follow-up period was small (n=28 breast cancers in the surveillance group and 19 breast cancers in the surgery group)
[21] The total numbers in the study were small (n=302 treated with breast conserving therapy and 353 treated with mastectomy); numbers for recurrence were not reported
[22]Kauff *et al.,* (2008)
[23]Pierce *et al.,* (2010)

Cost effectiveness evidence (2013)

A literature review of published cost-effectiveness analysis did not identify any relevant papers. No further health economic analysis was undertaken although testing at diagnosis compared with delayed testing could have a potentially significant economic and resource impact, the quality of available data did not lend itself to modelling.

Recommendations

- Do not offer fast track genetic testing (within 4 weeks of a diagnosis of breast cancer) except as part of a clinical trial. **[new 2013]**
- Offer people eligible for referral to a specialist genetics clinic a choice of accessing genetic testing during initial management or at any time thereafter. **[new 2013]**
- Discuss the individual needs of the person with the specialist genetics team as part of the multidisciplinary approach to care. **[new 2013]**

Linking Evidence to Recommendations

The aim of this topic was to determine whether knowing the mutation status (*BRCA1, BRCA2* and *TP53*) of a patient (who meets the threshold for genetic testing) within 4 weeks of diagnosis of their first breast cancer can usefully inform immediate decisions about breast cancer treatment or future surveillance to achieve better long term outcomes.

The topic was developed to investigate whether the proportion of eligible patients with newly diagnosed breast cancer who received targeted therapy (chemotherapy, radiotherapy, surgery) and/or who underwent risk-reducing surgery differed according to whether the patients were known *BRCA1*/2 carriers or not.

The outcomes considered to be of most importance included response to targeted treatments, disease specific survival, recurrence and health related quality of life for each treatment type as well as patient satisfaction with their treatment choice. Neither health related quality of life or patient satisfaction were reported in the evidence. The quality of the evidence was very low for all outcomes on GRADE assessment.

The GDG agreed there was insufficient evidence to say whether knowledge of mutation status before making decisions about risk-reducing mastectomy influenced outcome. The populations in each of the included studies varied slightly in relation to timing of genetic testing and knowledge of test results and therefore these data could not be compared and pooled. In addition only one study was carried out in a UK population. No study reported on whether knowledge of mutation status before making a decision on breast conserving therapy influenced outcome.

There was no evidence that a delay in genetic testing at diagnosis of breast cancer affected overall survival and so the GDG decided not to recommend fast track genetic testing (within 4 weeks of diagnosis) outside the context of a clinical trial because the evidence of clinical benefit was lacking. The GDG were unwilling to make recommendations that would require significant changes in practice based on such limited evidence.

The GDG felt the current pathway gives patients time to make an informed choice of whether to be referred or not, allow them to discuss the implications of a mutation potentially being detected with other family members and it was also noted that fast track referral may limit the options in terms of choice of surgeon and reconstructive procedure. Another consideration was the conflation of decisions about surgery for cancer treatment and surgery

as a future risk-reducing procedure leading to potentially hasty decision making about extensive surgery.

The GDG noted however that current advice for people of Jewish origin would allow them access to genetic testing within two weeks, but, as outlined above, the GDG were unsure if there would be any clinical advantage by fast tracking a person who did not have a clear family history of breast or ovarian cancer already.

However the GDG were careful to include a recommendation that allowed eligible people with a significant family history of breast or ovarian cancer and eligible people based on a probability of being a gene carrier to be referred at initial management or at some point in the future, including during the course of their cancer treatment.

The GDG also agreed, based on their clinical experience, that the individual needs of the person should be discussed with a specialist genetics team as part of the multidisciplinary approach to care.

The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG agreed that there would be neither additional costs nor savings as a result of these recommendations as they are not recommending a change in current practice.

The GDG agreed that there is a need to carefully weigh up the harms and benefits of fast track testing. Therefore the GDG decided to recommend further research in this area in order to compare the existing service model with a model providing rapid access to genetic testing. Because of the uncertainty and lack of evidence highlighted by this topic the GDG agreed that research should focus on describing an optimal service delivery model for patients newly diagnosed with breast cancer and a family history, the cost effectiveness of such a change and patient experience and uptake.

Research recommendation

- Research is recommended to determine the benefits and harms of creating rapid access to genetic testing for people with newly diagnosed breast cancer. This research should address the optimum model for service delivery and organisation, the clinical and cost effectiveness of such a change, uptake outcomes and patients' experience. **[new 2013]**

6.5 Discussing the outcomes of genetic testing

If tailoring cancer treatment and future surveillance options on the basis of *BRCA* and *TP53* mutation status leads to improved outcomes, there may be an argument for offering genetic testing to newly-diagnosed breast cancer patients who reach a predetermined carrier probability threshold.

Genetic testing for breast cancer patients raises several practical and ethical issues. The object of this topic was to identify who should provide patients with information about the outcome of genetic tests carried out soon after their diagnosis in order to inform treatment and follow-up.

In current practice these discussions are undertaken before and after genetic testing by someone with appropriate training. In reality this usually means a genetics specialist (genetic counsellor or clinical geneticist).

If patients are to have genetic tests within four weeks of diagnosis it may not be practical for them to be seen by a genetics specialist to discuss the results due to limited numbers of suitably trained geneticists. Conceivably, patients may request rapid testing and results could be given by any member of the multidisciplinary team if they have adequate training in the interpretation and communication of genetic test results. How the adequacy of knowledge level should be measured and assessed is unclear at present, in the absence of formal clinical genetics training. However discussion of genetic test results could conceivably include the GP, surgical specialist, breast care nurse or oncologist. The risk of widely differing interpretations of the pre and post test information being conveyed to the individual who has been tested may support an argument for recommending a particular member of the MDT to discuss the results of genetic testing with patients.

Clinical Question: Who should discuss the implications of genetic testing with the patient and when is the most appropriate time for such a discussion to occur?

Clinical Evidence (2013) (see also full evidence review)

Evidence Statements

Very low quality evidence (Brown, *et al.,* 2005; Table 6.23) suggests the majority of women are satisfied with the information they receive during genetic counselling. In this study satisfaction was highest among women who had been counselled by a genetics professional compared with a non-professional (98.5% versus 72.2%; p=0.0013).

One qualitative study (Arden-Jones, *et al.,* 2005) exploring patient preference about which health professional they would like to discuss genetic testing with reported that the women agreed that how the information was delivered was very important. They wanted someone who had time and was an expert in the field with the majority of women preferring the information to be presented by a member of the genetics team.

There was no evidence about the impact of who discusses genetic testing on the dissemination of information to family members, improved decision making or patient understanding.

Table 6.23: GRADE Profile: Who should discuss the implications of genetic testing with the patient and when is the most appropriate time for such a discussion to occur?

Quality assessment							Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
Patient satisfaction with counselling							
(Brown *et al.*, (2005)							
1	observational studies	serious[1]	no serious inconsistency	very serious[2]	serious[3]	none	VERY LOW
Patient Preference							
Arden-Jones *et al.*, (2005)							
1	observational study	serious[1]	no serious inconsistency	serious[4]	serious[3]	none	VERY LOW

[1] This was a retrospective survey study with patient reported outcomes, and is therefore prone to participant recall bias. There was a high risk of selection bias due to the population from which participants were recruited

[2] The average time passed since diagnosis was 2 years 11 months (Range = 1 – 81 months) which suggests many participants were recently diagnosed. However, there is no data about time between breast cancer diagnosis and referral to genetic counselling which limits the relevance of this study to the PICO.

[3] This study had a small sample size, of which only a minority actually received genetic testing (n=90), which reduces the precision of the data.[4]referred to receiving information about genetic testing after a diagnosis of breast cancer, rather than the discussion of genetic test results

Cost effectiveness evidence (2013)

A literature review of published cost-effectiveness analysis did not identify any relevant papers. No further health economic analysis was undertaken as the topic did not lend itself to economic evaluation due to a lack of comparison of costs and benefits.

Recommendation

- Offer detailed consultation with healthcare professionals who have appropriate up-to-date genetic knowledge and training to all those who are offered genetic testing, regardless of the time frame for testing. **[new 2013]**

Linking Evidence to Recommendations

The aim of this topic was to determine who should discuss the outcomes of genetic testing with a patient and when this discussion should take place.

The outcomes considered to be of most importance to this topic included the dissemination of information to a patient's family members, the improvement to decision making, patient understanding and comprehension and patient satisfaction, including surgical and treatment satisfaction. The GDG agreed to consider an additional outcome of patient preference reported in one study. .. However no evidence was available directly investigating any of the other outcomes.

The quality of the evidence for the reported outcome was very low on GRADE assessment. The evidence only reported patient satisfaction with the information they received during counselling for genetic testing after a diagnosis of breast cancer, rather than the results of the genetic test or the timing of these discussions. However, this qualitative study was limited because patients were only asked retrospective and hypothetical questions and therefore the results could only be considered as indirect evidence. Therefore the GDG agreed to base their recommendations on their clinical experience.

The GDG agreed, based on their clinical experience, that patients need to be able to make informed choices and decisions regarding genetic testing and so recommended that a detailed consultation with healthcare professionals who has appropriate up to date genetic knowledge and training should be offered to all those who are offered genetic testing, regardless of the time frame for testing.

The GDG felt the recommendation would give patients all the necessary information, in a timely manner, about the implications of genetic testing, to allow them to make an informed choice of whether to be referred or not and allow them to discuss the implications of a mutation potentially being detected with other family members.

The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG agreed that there would be neither additional costs nor savings as a result of these recommendations as they are not recommending a change in current practice.

The GDG agreed that a research recommendation should be included to determine who should discuss fast track genetic testing with newly diagnosed patients, the optimum way of providing the information, the psychosocial impact of receiving information on genetic testing within four weeks of a breast cancer diagnosis and also the impact of undergoing testing in the short, medium and long term.

Research Recommendation

- Research is recommended as part of a trial of fast track genetic testing to determine:
  - which members of the multidisciplinary team should/could discuss fast track testing with people with newly diagnosed breast cancer
  - the best way of providing information about fast track genetic testing to people with newly diagnosed breast cancer
  - the psychosocial impact of receiving information about genetic testing within 4 weeks of a diagnosis of breast cancer
  - the short, medium and long-term psychosocial impact of undergoing fast track genetic testing.**[new 2013]**

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7 Surveillance and strategies for early detection of breast cancer

People who are at increased risk of developing breast cancer due to their family history may reduce the potential consequences (morbidity or mortality) related to any incident cancer through early detection. This chapter aims to specify the optimal strategy for people who are at increased risk of breast cancer due to their family history but with no personal history of breast cancer, and people who have an increased risk due to their family history and who have had breast cancer but have not undergone bilateral mastectomy**.**

7.1 Breast awareness

Most cases of breast cancer are found by a person noticing unusual changes and taking the initiative by visiting their doctor. The earlier breast cancer is found, the better the chance of treating it successfully so it is important to emphasise the value of making regular checks.

Being breast aware means a person knowing what their breasts normally look and feel like, being on the lookout for any unusual changes and reporting any changes to their doctor. It is important to realise that there are a number of significant signs to look out for in addition to a lump.

Clinical Evidence (2004) (see also full evidence review)

No evidence was identified for the effectiveness of either clinical or self-breast examination as the sole screening modality in women with a family history of breast cancer and/or *BRCA1*/2 mutations.

A 2003 Cochrane Review which examined the evidence for regular self-examination or clinical examination for early detection of breast cancer (for women in general), concluded that trials did not suggest a beneficial effect of screening by breast examination, and may in some instances cause harm (Koster & Gotzsche, 2003).

Furthermore, the Department of Health issued advice that clinical breast examination was not an appropriate screening technique in February 1998. The reference is PL/CMO/98/1.

Evidence Statement (2004)

There is a lack of evidence for a high risk population that either clinical breast examination or self-examination is useful as the sole surveillance modality. (III)

Recommendation

- Women at increased risk of breast cancer should be 'breast aware' in line with Department of Health advice for all women.[21] **[2004]**

[21] www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_062697

7.2 Surveillance for women with no personal history of breast cancer

Women at increased risk of developing breast cancer due to their family history can opt to have surveillance in order to detect a cancer when it is small and ideally before it has spread to other parts of the body. Women at sufficiently high risk may opt for risk-reducing bi-lateral mastectomy as an alternative.

Studies in women at population risk for breast cancer have shown that early detection confers a survival advantage. This may also be the case for women at increased risk. Although MRI has been shown to be more sensitive at early detection of breast cancer in the high risk group, we cannot confirm whether this confers a survival benefit. The risk of surveillance is that the test may be positive when no disease exists (false positive) resulting in additional tests being performed to confirm there is no disease as well as causing distress for the woman. Some tests have higher false positive rates than others.

Previous NICE guidance only recommended enhanced surveillance between the ages of 30 and 49. There was no specific recommendation for surveillance in the high risk group after the age of 50, which has led to widespread variation in practice. Although recommendations were made for women at moderate risk, aged 40-49, application of this has been inconsistent. There has also been concern amongst women at moderate risk about cessation of enhanced screening at aged 50 years.

Clinical Question: What are the specific surveillance needs of women with a family history who have no personal history of breast cancer?

Clinical Evidence for the diagnostic accuracy of screening (2013) (see also full evidence review)

Study Quality (Diagnostic Outcomes)

Evidence about MRI, mammography, clinical breast examination and ultrasound for surveillance women at high familial risk of breast cancer or with a proven mutation was drawn from a systematic review (Warner *et al.,*, 2008) of 11 studies (Hagen, *et al.,* 2007; Hartman, *et al.,* 2004; Kriege, *et al.,* 2004; Kuhl, *et al.,* 2005; Leach, *et al.,* 2005; Lehman, *et al.,* 2005; Lehman, *et al.,* 2007; Sardanelli, *et al.,* 2007; Trecate, *et al.,* 2006; Warner, *et al.,* 2001; Warner, *et al.,* 2004) and three other studies (Riedl, *et al.,* 2007; Trop, *et al.,* 2010; Halapy, *et al.,* 2005).

Assessment of surveillance imaging was blinded in 12/14 of these studies; all were prospective. The MARIBS (Leach, *et al.,* 2005), MRISC (Kriege, *et al.,* 2004) and Halapy, *et al.,* (2005) studies excluded women with a personal history of breast cancer but approximately one third of those included in the other studies had a personal history of breast cancer. In all studies the reference standard for a positive surveillance test was biopsy and histopathology, for negative screening tests the reference standard was clinical and radiological follow up. (see table 7.1)

1 **Table 7.1**:- Methodological quality of included studies

	Representative spectrum?	Acceptable reference standard?	Acceptable delay between tests?	Partial verification avoided?	Differential verification avoided?	Incorporation avoided?	Reference standard results blinded?	Index test results blinded?	Relevant clinical information?	Withdrawals explained?
MRISC trials (Kriege, *et al.,* 2003, 2004, 2006, 2006; Rijnsburger, *et al.,* 2007, 2010)*	Yes	Yes[b]	Yes	Yes	No[c]	Yes	No	Yes	Yes	Yes
Kuhl, *et al.,* 2005*	Yes	Yes[b]	Yes	Yes	No[c]	Yes	No	Yes	Yes	Yes
Leach, *et al.,* (2005)* **MARIBS**	Yes	Yes[b]	Yes	Yes	No[c]	Yes	No	Yes	Yes	Yes
Warner, *et al.,* (2001)*	No	Yes[b]	Yes	Yes	No[c]	Yes	No	Yes	Yes	Yes
Warner, *et al.,* (2004)*	No	Yes[b]	Yes	Yes	No[c]	Yes	No	Yes	Yes	Yes
Trecate, *et al.,* (2006)*	No	Yes[b]	Yes	Yes	No[c]	Yes	No	?	Yes	Yes
Hartman, *et al.,* (2004)*	No	Yes[b]	Yes	Yes	No[c]	Yes	No	?	Yes	Yes
Lehman, *et al.,* (2005)*	No	Yes[b]	Yes	Yes	No[c]	Yes	No	Yes	Yes	Yes

	Representative spectrum?	Acceptable reference standard?	Acceptable delay between tests?	Partial verification avoided?	Differential verification avoided?	Incorporation avoided?	Reference standard results blinded?	Index test results blinded?	Relevant clinical information?	Withdrawals explained?
Lehman, *et al.,* (2007)*	No	Yes[b]	Yes	Yes	No[c]	Yes	No	Yes	Yes	Yes
Sardinelli, *et al.,* (2007)*	No	Yes[b]	Yes	Yes	No[c]	Yes	No	Yes	Yes	Yes
Hagen, *et al.,* (2007)*	No	Yes[b]	Yes	Yes	No[c]	Yes	No	Yes	Yes	Yes
Riedl, *et al.,* (2007)	No	Yes[b]	Yes	Yes	No[c]	Yes	No	Yes	Yes	Yes
Trop, *et al.,* (2010)	No	Yes[b]	Yes	Yes	No[c]	Yes	No	Yes	Yes	Yes
Halapy ,*et al.,* 2005	No[a]	Yes[b]	Yes	Yes	No[c]	Yes	No[c]	Yes	Yes	Yes

[a] Included only women over 50 years
[b] All breast cancers were histologically confirmed
[c] Only those screening positive received the reference test

*Included in Warner, *et al.,* (2008) systematic review

Evidence statements (Diagnostic Outcomes)

Moderate quality evidence suggests surveillance using MRI has better sensitivity for breast cancer than mammography, clinical breast examination or ultrasound. Surveillance with both MRI and mammography has better sensitivity than either test alone (Warner, *et al.,* 2008).

The Warner, *et al.,* (2008) systematic review estimated breast cancer prevalence amongst high risk women undergoing surveillance as approximately 2%. Using their pooled sensitivities and specificities the results from 1000 combined MRI and mammography surveillance tests would include 17 true positives, 49 false positives, 931 true negatives and 3 false negatives (see table 7.2).

Rijnsburger, *et al.,* (2010) analysed the relative sensitivity of mammography and MRI surveillance in three age groups: less than 40 years, 40 to 49 years and 50 or older. MRI had better sensitivity than mammography in all three groups: 61% versus 33%, 83% versus 39% and 67% versus 56% respectively.

Table 7.2: Diagnostic accuracy of surveillance mammography, MRI, ultrasound and clinical breast examination in women at high risk of breast cancer

Test	Test threshold	Studies	Breast cancers diagnosed	Sensitivity	Specificity	PPV	NPV
Mammography	BI-RADS ≥ 3	(Kriege, *et al.,* 2004; Kriege, *et al.,* 2004; Leach, *et al.,* 2005; Lehman, *et al.,* 2007; Warner, *et al.,* 2004)	108 tumours / 6678 screens	39% (95% C.I. 37 to 41%)*	95% (95% C.I. 93 to 97%)*	15% (95% C.I. 8 to 26%)†	1.3% (95% C.I. 1.1 to 1.5%)†
Mammography	BI-RADS ≥ 4	(Kriege, *et al.,* 2004; Kuhl, *et al.,* 2005; Leach, *et al.,* 2005; Lehman, *et al.,* 2005; Sardanelli, *et al.,* 2007; Trecate, *et al.,* 2006; Warner, *et al.,* 2004)	178 tumours / 8818 screens	32% (95% C.I. 23 to 41%)*	99% (95% C.I. 98 to 99%)*	34% (95% C.I. 19 to 52%)†	1.4% (95% C.I. 1.2 to 1.6%)†
MRI	BI-RADS ≥ 3	(Hartman, *et al.,* 2004; Kriege, *et al.,* 2004; Leach, *et al.,* 2005; Lehman, *et al.,* 2007; Warner, *et al.,* 2004)	109 tumours / 6719 screens	77% (95% C.I. 70 to 84%)*	86% (95% C.I. 81 to 92%)*	8% (95% C.I. 6 to 11%)†	0.6% (95% C.I. 0.4 to 0.8%)†
MRI	BI-RADS ≥ 4	(Hartman, *et al.,* 2004; Kriege, *et al.,* 2004; Kuhl, *et al.,* 2005; Leach, *et al.,* 2005; Lehman, *et al.,* 2005; Sardanelli, *et al.,* 2007; Trecate, *et al.,* 2006; Warner, *et al.,* 2004)	178 tumours / 8857 screens	75% (95% C.I. 62 to 88%)*	96% (95% C.I. 95 to 97%)*	25% (95% C.I. 18 to 34%)†	0.4% (95% C.I. 0.2 to 0.9%)†
Mammography + MRI	BI-RADS ≥ 3	(Lehman, *et al.,* 2007; Warner, *et al.,* 2001; Warner, *et al.,* 2004)	63 tumours/ 2509 screens	94% (95% C.I. 90 to 97%)*	77% (95% C.I. 75 to 80%)*	8% (95% C.I. 7 to 9%)†	0.2% (95% C.I. 0.08 to 0.4%)†
Mammography + MRI	BI-RADS ≥ 4	(Kuhl, *et al.,* 2005; Leach, *et al.,* 2005; Lehman, *et al.,* 2007; Trecate, *et al.,* 2006; Warner, *et al.,* 2004)	115 tumours/ 4272 screens	84% (95% C.I. 70 to 97%)*	95% (95% C.I. 94 to 97%)*	25% (95% C.I. 18 to 33%)†	0.3% (95% C.I. 0.1 to 0.8%)†
Clinical Breast Examination	NR	(Halapy, *et al.,* 2005; Rijnsburger, *et al.,* 2010; Sardanelli, *et al.,* 2007; Trop, *et al.,* 2010; Warner, *et al.,* 2004)	157/12325 patients	9% to 50%	94% to 99%	4% to 81%	0.4% to 8.7%
Ultrasound	BI-RADS ≥ 4	(Riedl, *et al.,* 2007; Trecate, *et al.,* 2006; Trop, *et al.,* 2010; Warner, *et al.,* 2004)	116/2971 patients	32% to 60%	91% to 100%	10% to 100%	1.8% to 4.2%
Mammography + Ultrasound	BI-RADS ≥ 4	(Kuhl, *et al.,* 2005)	43/529 patients	52%	89%	12%	1.4%

Abbreviations: BI-RADS, Breast Imaging, Reporting and Data System; NR, not reported; MRI, magnetic resonance imaging; PPV, positive predictive value; NPV, negative predictive value.
*Results from separate univariate meta-analyses of sensitivity and specificity (Warner, *et al.,* 2008). †Assuming 2% pre-test probability of breast cancer (Warner, *et al.,* 2008).

Evidence statements (Clinical Outcomes)

Stage at Detection

Very low quality evidence from two studies (see table 7.3) suggests that invasive breast cancers diagnosed in mammography screened women aged 50 years or less with family history of breast cancer are significantly smaller than those diagnosed in unscreened women of similar age (Maurice, *et al.,* 2006; Duffy, *et al.,* 2010). In these two studies 28 to 30% of invasive tumours diagnosed during screening were greater than 2 cm in diameter, this compared to 45 to 61% of tumours diagnosed in the unscreened comparison groups.

Very low quality evidence from two studies suggests women aged 50 or less with family history of breast cancer whose invasive breast cancer was diagnosed during screening were less likely to have positive nodes at diagnosis than unscreened women of similar age diagnosed with breast cancer (Maurice, *et al.,* 2006; Duffy, *et al.,* 2010). In these two studies 32 to 34% women diagnosed with invasive breast cancer during screening had positive nodes, this compared to 47 to 53% of those diagnosed in the unscreened comparison groups.

Disease Specific Survival

Very low quality evidence suggests a disease specific survival benefit with mammographic surveillance in women aged less than 50 years with a family history of breast cancer.

In Maurice, *et al.,* (2006) death from breast cancer was less likely in women aged less than 50 years with family history whose breast cancer was diagnosed during mammographic surveillance than in a control group of unscreened women of similar age who developed breast cancer (lead time adjusted HR 0.24 [95% CI 0.09 to 0.66]).

Duffy, *et al.,* (2010) modelled death from breast cancer in a mammographic surveillance study in women with a family history aged less than 50 years and a control group from another study, using prognostic features at diagnosis and underlying risk. Projected ten year death from breast cancer was lower in the mammographic surveillance group than in the control group of unscreened women of similar age, RR 0.80 (95% CI 0.66 to 0.96).

In Maurice, *et al.,* (2012) death from any cause was less likely in *BRCA1/2* carriers aged between 28 and 77 years diagnosed with breast cancer during an intensive mammographic surveillance programme than in those diagnosed outside this programme (HR 0.44 [95% CI 0.25 to 0.77]). It was unclear, however, whether this estimate was adjusted for lead time bias.

Incidence of breast cancer, Incidence of Radiation Induced Breast Cancer

Low quality evidence, from case-control studies (Jansen, *et al.,* 2010), suggests that exposure to low dose radiation during screening mammography or chest X-ray is associated with an increased risk of breast cancer in women with a familial or genetic predisposition, OR 1.3 (95% C.I. 0.9 to 1.8). There was evidence of a dose-response relationship between low dose radiation and breast cancer in this population: exposure to low dose radiation before the age of 20 years (OR 2.0; 95% C.I. 1.3 to 3.1) and five or more exposures (OR 1.8; 95% C.I. 1.1 to 3.0).

Health Related Quality of Life (HRQOL)

Low quality evidence suggests that screening with biannual Clinical Breast Examination (CBE), annual mammography, annual Magnetic Resonance Imaging (MRI), and

recommendations for monthly Breast Self-Examination (BSE) has no unfavourable impact on generic short-term HRQOL (Rijnsberger, *et al.,* 2004).

Rijnsberger, *et al.,* (2004) recorded pain, discomfort and anxiety experienced by women at high risk of breast cancer during screening tests. The proportion of women who reported pain was 7%, 86% and 12% during CBE, mammography and MRI respectively; 9%, 69% and 45% of women experienced discomfort during CBE, mammography and MRI respectively; 22%, 28% and 37% of women experienced anxiety during CBE, mammography and MRI respectively.

Table 7.3: GRADE Profile: What is the effectiveness of surveillance in women at increased risk of breast cancer but with no personal history?

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surveillance mammography	No surveillance mammography	Relative (95% CI)	Absolute	
Size of tumour at diagnosis > 2cm (in women diagnosed with invasive breast cancer; Maurice, *et al.,* 2006; Duffy *et al.*,, 2010)											
2	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	38/130 (29.2%)	813/1531 (53.1%)	not pooled	not pooled	VERY LOW
Positive nodes at diagnosis (in women diagnosed with invasive breast cancer; Maurice, *et al.,* 2006; Duffy *et al.*,, 2010).											
2	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40/123 (32.5%)	774/1521 (50.9%)	not pooled	not pooled	VERY LOW
Death from breast cancer (in women diagnosed with breast cancer, younger than 50 years; Maurice, *et al.,* ,2006)											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	4/62 (6.5%)	210/898 (23.4%)	HR 0.24 (0.09 to 0.66)	172 fewer per 1000 (from 73 more to 210 more)	VERY LOW
Death from any cause (in *BRCA1/2* carriers diagnosed with breast cancer within intensive versus population screening programmes; Maurice *et al.,* ,2012)											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	4/45 (8.8%)	N.R./466	HR 0.44 (0.25 to 0.77)	NR	VERY LOW
Projected ten year breast cancer mortality (FH01 – Duffy, *et al.,* 2010)											
1	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	73/6710 (1.1%)	1461/106971 (1.4%)	RR 0.80 (0.66 to 0.96)	3 fewer per 1000 (from 1 fewer to 5 fewer)[3]	VERY LOW
Breast cancer following exposure to low dose radiation (chest X-ray or mammography) among women with a familial or genetic predisposition (Jansen, *et al.,* 2010)											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surveillance mammography	No surveillance mammography	Relative (95% CI)	Absolute	
7	observational studies	no serious risk of bias	serious[4]	no serious indirectness	no serious imprecision	dose response gradient[5]	5132 cases	11592 controls	OR 1.3 (0.9 to 1.8)	-	LOW
Breast cancer following exposure before 20 years of age to low dose radiation (chest X-ray or mammography) among women with a familial or genetic predisposition (Jansen, *et al.,* 2010)											
2	observational studies	no serious risk of bias	serious[4]	no serious indirectness	no serious imprecision	dose response gradient[5]	-[6]		OR 2.0 (1.3 to 3.1)	-	LOW
Breast cancer following 5 or more exposures to low dose radiation (chest X-ray or mammography) among women with a familial or genetic predisposition (Jansen, *et al.,* 2010)											
4	observational studies	no serious risk of bias	serious[4]	no serious indirectness	no serious imprecision	dose response gradient[5]	-[6]		OR 1.8 (1.1 to 3.0)	-	LOW
Health related quality of life (Rijnsberger, *et al.,* 2004)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	334 women were screened (CBE, mammography and MRI) and their scores compared to a reference value from general population.		-	-	LOW

[1] The screened and unscreened cohorts were drawn from different sources - so factors other than screening may contribute to differences in outcome.
[2] Survival outcomes were not measured directly but predicted using prognostic models.
[3] Duffey, *et al.,* (2010) estimate that for every 10,000 screens (1000 women screened for ten years) there would be 2 breast cancer deaths prevented.
[4] Considerable heterogenity - one study (Andrieu, *et al.,* 2006) reported a much greater effect size than the others.
[5] Some evidence of a dose-response effect - younger age at first exposure and 5 or more exposures to radiation had a greater odds ratio for breast cancer.
[6] total number of women in this subgroup not reported

Cost effectiveness evidence (2013) (see also full cost effectiveness evidence review)

A literature review of published cost effectiveness analyses identified five relevant papers for inclusion for this topic (Griebsch, *et al.,* 2006, Plevritis, *et al.,* 2006, Moore, *et al.,* 2009, Taneja, *et al.,* 2009, Lee, *et al.,* 2010). The decision to offer certain types/frequencies of surveillance will impact on NHS resources and patient benefits and was identified as a high economic priority. However, results reported in the published literature were inconsistent and due to different comparators, risk groups and age groups difficult to compare.

Study quality and results

Five studies were included for this topic. All papers were deemed partially applicable to the guideline with very serious limitations. The reasons for partial applicability were that the analyses were conducted in countries other than the UK or they did not conform to one or more aspects of the NICE reference case. The results for all included studies are summarised in table 7.4.

Evidence statements

The evidence review for this topic included five papers which reported the cost-effectiveness of different screening strategies compared to no screening or each other. Four studies were conducted in the USA (Plevritis, *et al.,* 2006, Moore, *et al.,* 2009, Taneja, *et al.,* 2009, Lee, *et al.,* 2010) and one was based in a UK healthcare setting (Griebsch, *et al.,* 2006). The papers report varying degrees of cost-effectiveness and inconsistent results of cost-effectiveness of the different screening strategies.

Griebsch, *et al.,* (2006) reported results of a population of women aged 35-49 years at high genetic risk of breast cancer (>0.9%per annum) who were tested carriers of *BRCA1/2* or *TP53* mutations, a first-degree relative of someone with a mutation or could demonstrate a strong family history of breast or ovarian cancer. Lee, *et al.,* (2010) modelled cost-effectiveness of screening for initially 25-year old *BRCA1* carriers whereas Plevritis, *et al.,* (2006) included 25-year old *BRCA1* and *BRCA2* carriers in their model. Moore, *et al.,* (2009) looked at a hypothetical cohort of women with a strong family history of breast cancer and Taneja, *et al.,* (2009) investigated cost-effectiveness of screening in a simulated cohort of 40-year old women with *BRCA1/2* mutation or a strong family history.

Griebsch, *et al.,* (2006) compared annual screening with a combined approach of MRI and mammography to mammography recall alone while Moore *et al.,* (2009) compared annual mammography with MRI only and Plevritis, *et al.,* (2006) investigated the cost-effectiveness of MRI and the combined approach against no screening. Lee, at al., (2010) looked at annual film-screen mammography, annual MRI and annual combined approach in comparison to clinical examination. Taneja, *et al.,* (2009) estimated the cost-effectiveness of a single event of MRI and the combined approach when compared to mammography.

Griebsch, *et al.,* (2006) did not report cost/QALY results but calculated that the combined approach cost £34,951.33 per additional cancer detected (converted to 2011 GPB). They concluded that assuming a willingness to pay of £20,000 MRI+XRM only had 0.07 probability of being cost-effective and 0.67 cost effective when the threshold was raised to £30,000. Lee, *et al.,* (2010) found that compared to clinical surveillance mammography had an ICER of £12,076.57, MRI of £148,791.75 and the combined approach cost £49,835.40/QALY gained (converted to 2011 GPB). Moore, *et al.,* (2009) concluded that MRI was not cost-effective when compared to mammography in people with a strong family history while Plevritis, *et al.,* (2006) found that mammography is cost-effective for *BRCA1/2* carriers up to 69 years and MRI is cost-effective for *BRCA1* carriers up to 49 years of age. In

contrast, Taneja, *et al.,* (2009) suggested that MRI and the combined approach were cost-effective compared to mammography. Effectiveness data used in Griebsch *et al.,* (2006) was derived from a single multi-centre prospective study, whereas Lee *et al.,* (2010) Moore *et al.,* (2009) and Taneja, *et al.,*(2009) used data from published literature and Plevritis, *et al.,* (2006) and used Surveillance epidemiology and end results (SEER) data.

Table7.4: Economic evidence profile: What are the specific surveillance needs of women with a family history who have no personal history of breast cancer?

Quality assessment			***Summary of findings***						
Study	*Limitations*	*Applicability*	*Population*	*Intervention*	*Comparator*	*Incremental cost (2011 £)*	*Incremental effects*	*ICER*	*Uncertainty*
Griebsch, 2006	Very serious limitations [1]	Partially applicable [2]	Women aged 35-49 years at high genetic risk of breast cancer who were: Tested carriers of *BRCA1/2* or *TP53* mutation; first degree relative of someone with above mutation or strong family history of breast or ovarian cancer.	Annual screening with CE MRI and both CE MRI and XRM	Recall by XRM alone	Compared to mammography alone:[3] MRI: £324.13 MRI+XRM: £371.58	Number of cancers detected per screen compared to mammography: MRI: 0.00744 MRI+XRM: 0.01063	MRI+XRM £34,951.33 per additional cancer detected [4]	Assuming a willingness to pay of £20,000 MRI+XRM 0.07 probability of being cost-effective. When raised to £30,000 cost effective was 0.67.
Lee 2010	Very serious limitations [5]	Partially applicable [6]	25 year old *BRCA1* mutation carriers	Annual screening strategies of Screen film mammography MRI Mammography and MRI	Clinical surveillance	Compared to strategy mentioned before:[7] Clinical surveillance: - Mammography: £3095.74 MRI: £5987.46 Combination: £1681.25	Incremental QALYs Compared to strategy mentioned before: Clinical surveillance: - Mammography 0.25 MRI 0.04 Combined 0.12	Mammography £12,076.57 MRI eliminated-£148,791.75 Combined £49,835.40 [8]	Univariate analysis included mutation penetrence, diagnostic test, costs of screening, discount and quality of life weights, sensitivity/specificity value of screening and effect of risk-reducing

Quality assessment			***Summary of findings***						
Study	*Limitations*	*Applicability*	*Population*	*Intervention*	*Comparator*	*Incremental cost (2011 £)*	*Incremental effects*	*ICER*	*Uncertainty*
									BSO
Moore 2009	Very serious limitations [9]	Partially applicable [10]	Hypothetical cohort of women with >-15% cumulative risk based on Claus criteria (strong family history)	Annual breast screening XRM MRI	Each other	Of MRI compared to mammography: £9950.20 [11]	Incremental QALYs of MRI compared to mammography: 0.1	MRI: £133,292.02 [12]	PSA: MRI superior in 0% <$50,000 per QALY, 22% >$50,000 per QALY; MRI not cost-effective

Quality assessment			***Summary of findings***						
Study	*Limitations*	*Applicability*	*Population*	*Intervention*	*Comparator*	*Incremental cost (2011 £)*	*Incremental effects*	*ICER*	*Uncertainty*
Plevritis 2006	Very serious limitations [13]	Partially applicable [14]	Simulated cohort of female 25 year old *BRCA1/2* mutation carriers with no prior history and no prior prophylactic mastectomy or chemoprevention	Mammography + MRI; Mammography alone	No screening	Compared to no screening:[15] *BRCA1* Mammography (25-69 years): £2420.86 MRI (40-49 years): £4841.72 MRI (25-69 years): £4708.37 *BRCA2* Mammography (25-69 years): £2460.71 MRI (40-49 years): £5224.12 MRI (25-69 years): 4680.02	Incremental QALYs compared to no screening: *BRCA1* Mammography (25-69 years): 0.167 MRI (40-49 years): 0.145 MRI (25-69 years): 0.013 *BRCA2* Mammography (25-69 years): 0.113 MRI (40-49 years): 0.061 MRI (25-69 years): 0.008	Compared to no screening:[16] *BRCA1* Mammography (25-69 years): £14,523.62/QALY MRI (40-49 years): £33,323.39/QALY MRI (25-69 years): £364,724.25/QALY *BRCA2* Mammography (25-69 years): £21,780/QALY MRI (40-49 years): £85,523.2/QALY MRI (25-69 years): £560,616.06/QALY	MRI becomes more cost effective as risk increases and less cost-effective as risk decreases.. For women aged 50 years and younger with extremely dense breast adds $41,183 per QALY for *BRCA1* and $98,454 per QALY for *BRCA2*. It is sensitive to cost of MRI – sensitive to discounting.

Quality assessment			***Summary of findings***						
Study	*Limitations*	*Applicability*	*Population*	*Intervention*	*Comparator*	*Incremental cost (2011 £)*	*Incremental effects*	*ICER*	*Uncertainty*
Taneja 2009	Very serious limitations [17]	Partially applicable [18]	Hypothetical cohort of women aged 40 years at high risk of undetected cancer, invasive or DCIS - *BRCA1 or 2* mutation carriers or strong family history with >20% life-time risk.	Single episode within established screening programme MRI XRM + MRI	XRM	Not stated	Not stated	Compared with mammography:[19] MRI: £19418.98/ QALY MRI+XRM: £19370.70/ QALY	Sensitivity to prevalence. *BRCA1/2*- $65,094 if prevalence 2% (Base case was 4%), $12,007 if 6%. *BRCA1 or 2* cost-effective for MRI alone or in combination compared with XRM alone.

[1] Effectiveness data is based on one single prospective study; no cost-utility analysis undertaken, no quality of life data considered. Therefore the relevance of these results for informing the current guideline is limited.
[2] The analysis does not meet one or more aspects of the NICE reference case.
[3,4] Converted from 2003 GPB using a PPP exchange rate of 1.00 then uprated by inflation factor of 124% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[5] Data is based on published literature; only *BRCA1* carriers considered, no cost inputs reported. Therefore the relevance of these results for informing the current guideline is limited.
[6] The analysis does not meet one or more aspects of the NICE reference case.
[7,8] Converted from 2007 US dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 112% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[9] Data is based on published literature; no distinguishing in different risk groups, costs not discounted but outcomes discounted at 5%. Therefore the relevance of these results for informing the current guideline is limited.
[10] The analysis does not meet one or more aspects of the NICE reference case.
[11,12] Converted from 2006 US dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 105% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[13] Cost and utility data is based on published literature; only *BRCA1* and *BRCA2* carriers considered, no PSA reported. Therefore the relevance of these results for informing the current guideline is limited.
[14] The analysis does not meet one or more aspects of the NICE reference case.
[15,16] Converted from 2005 US dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 108% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[17] Data sources not reported, no PSA reported, only single screening event considered. Therefore the relevance of these results for informing the current guideline is limited.
[18] The analysis does not meet one or more aspects of the NICE reference case.
[19] Converted from 2005 US dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 112% (http://eppi.ioe.ac.uk/costconversion/default.aspx).

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Recommendations (see also table 7.5)

- 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 claustrophobia)
    - for problem solving mammographically or MRI detected abnormalities . **[new 2013]**
- Offer annual mammographic surveillance to all women:
    - aged 40- 49 years at moderate risk of breast cancer.
    - aged 40 years and over at high risk of breast cancer. **[new 2013]**
- Offer annual mammographic surveillance to women aged 30-39 years at moderate or high risk of breast cancer only as part of an approved research study.**[new 2013]**
- Do not offer mammographic surveillance to women under 30 years and at moderate or high risk of breast cancer. **[new 2013]**
- Do not offer mammographic surveillance to women under 50 years with a *TP53* mutation or a greater than 30% probability of being a *TP53* carrier. **[new2013]**
- Offer mammographic surveillance as part of the population screening programme to women aged 50 years and over with a *TP53* mutation or a greater than 30% probability of being a *TP53* carrier. **[new 2013]**
- Consider annual mammographic surveillance for women aged 50 years and over at moderate risk of breast cancer. **[new 2013]**
- Offer annual MRI surveillance to all women:
    - aged 20-49 years with a *TP53* mutation
    - aged 20-49 years with a greater than 30% probability of being a *TP53* carrier
    - aged 30-49 years with a *BRCA1* or *BRCA2* mutation.
    - aged 30-49 years who have not had a genetic test but are at greater than 30% probability of being a *BRCA1* carrier. **[new 2013]**
- Do not offer MRI surveillance to women:
    - at moderate risk of breast cancer
    - at high risk of breast cancer unless they have a known BCRA1, BCRA2 or *TP53* mutation or a greater than 30% probability of being a*TP53* or BCRA1 carrier. **[new 2013]**
- Do not offer MRI surveillance to any women aged 50 years and over. **[new 2013]**
- 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[22]. **[new 2013]**
- Before decisions on surveillance are made, discuss and give written information on the risks and benefits of surveillance, including:
    - the possible reduced sensitivity of mammography in younger women with dense breasts and the increased likelihood of further investigations
    - possible over diagnosis
    - the risk associated with exposure to radiation

[22] 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)

  - the possible psychological impact of a recall visit. **[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]**
- 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. **[new 2013]**
- Ensure that women know the reasons for any changes to the surveillance plan**. [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]**
- 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]**
- Ensure that MRI surveillance includes MRI of both breasts performed to national breast screening programme standards. **[new 2013]**
- 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 MRI surveillance. (An example of an acceptable method is BOADICEA) **[new 2013]**
- Do not offer surveillance to women who have undergone a bilateral mastectomy**. [new 2013]**

Table 7.5: Summary of recommendations on surveillance for women with no personal history of breast cancer

Age	Group 1 Moderate risk of breast cancer[23]	Group 2 High risk of breast cancer[24] (but not fulfilling criteria for group 3, 4 or 5)	Group 3 Untested but greater than 30% *BRCA1* carrier probability [25]	Group 4 Known *BRCA1/2* carrier	Group 5 *TP53* mutation carriers[26] or greater than 30% *TP53* carrier probability
20-29	Do not offer mammography	Do not offer mammography	Do not offer mammography	Do not offer mammography	Do not offer mammography
	Do not offer MRI	Do not offer MRI	Do not offer MRI	Do not offer MRI	Annual MRI
30-39	Mammography only as part of an approved research study	Mammography only as part of an approved research study	Mammography only as part of an approved research study	Mammography only as part of an approved research study	Do not offer mammography
	Do not offer MRI	Do not offer MRI	Annual MRI	Annual MRI	Annual MRI
40-49	Annual mammography	Annual mammography	Annual mammography	Annual mammography	Do not offer mammography
	Do not offer MRI	Do not offer MRI	Annual MRI	Annual MRI	Annual MRI
50-59	Consider annual mammography	Annual mammography	Annual mammography	Annual mammography	Mammography as part of population screening programme
	Do not offer MRI	Do not offer MRI	Do not offer MRI	Do not offer MRI	Do not offer MRI
60+	Consider annual mammography	Annual mammography	Annual mammography	Annual mammography	Mammography as part of population screening programme
	Do not offer MRI	Do not offer MRI	Do not offer MRI	Do not offer MRI	Do not offer MRI

Linking evidence to recommendations

The aim of this topic was to determine the specific surveillance needs of women with a family history but who have no personal history of breast cancer. This topic updates the recommendations on surveillance from the previous guidance. The GDG examined the specific surveillance needs using evidence of both the diagnostic accuracy of surveillance methods and the clinical outcomes of individual surveillance methods.

The GDG considered sensitivity, specificity, positive predictive value and negative predictive value in a range of different age groups to be the most relevant outcomes for diagnostic accuracy. The GDG considered stage at detection, disease specific survival, incidence of breast cancer, incidence of radiation-induced cancer and health related quality of life to be the most important clinical outcomes. All these outcomes were reported in the evidence.

GRADE methodology was used to assess the quality of studies included within the clinical outcomes analysis. The quality of this evidence was low or very low for all outcomes on

[23] Lifetime risk of developing breast cancer is at least **17% but less than 30%**
[24] Lifetime risk of developing breast cancer is at least 30%
[25] Women who at first assessment had a 30%-50% *BRCA1* carrier probability and reach 50 years of age without developing breast cancer will now have a lower than 30% carrier probability
[26] Women who at first assessment had a 30%-or greater TP53 carrier probability and reach 50 years of age without developing breast cancer will now have a lower than 30% carrier probability and should no longer be offered MRI surveillance.

GRADE assessment. For studies included within the analysis of diagnostic accuracy, QUADAS assessment indicated that they were of good quality. Most of the studies were in people at high risk of breast cancer so the effectiveness of surveillance in those at moderate risk had to be extrapolated from this evidence.

The GDG assessed the recommendations from previous guidance in light of the updated evidence and made changes to these where appropriate. Where the evidence did not support making any changes, the GDG retained the recommendations from the previous guidance.

The GDG agreed that there was no new evidence to change the recommendation that ultrasound should not be used in routine surveillance practice for moderate and high risk women with no personal history of breast cancer. However for those individuals who cannot tolerate MRI the GDG agreed that ultrasound could be considered as an alternative surveillance tool.

The GDG agreed, based on their clinical experience, that additional guidance was needed on enhanced surveillance to enable the national breast screening programme to implement these recommendations. The GDG therefore added clarification of risk categories and age groups to the recommendations on surveillance.

The GDG agreed that the age at which mammographic surveillance should be available should remain at 30 years. In women under 30 years of age there is no evidence of effectiveness of mammography in detecting breast cancer and there continues to be a concern of the potential harm of radiation to young breast tissue and the incidence of radiation-induced cancers.

The GDG agreed not to amend the recommendation that women who are known to have a genetic mutation should be offered annual MRI surveillance if they are *BRCA*1 and *BRCA*2 mutation carriers aged 30–49 years. Although there was some evidence on MRI surveillance in individuals aged 50 and above the GDG concluded this was not sufficiently strong to increase the upper age limit.

When discussing the potential advantages and disadvantages of breast surveillance for early detection of breast cancer, the GDG agreed that the issue of over diagnosis should be included in the list of potential risks. The GDG noted there is continuing debate and controversy surrounding potential over diagnosis in the screening population and that these advantages and disadvantages should be explained to women.

As part of the surveillance of high risk women with MRI, the GDG agreed, based on their clinical experience, that MRI of both breasts should be performed to the standards of the national breast screening programme. These are high quality, nationally agreed standards that define the MRI protocol (acquisition and reading) and have a robust programme of audit.

The GDG concluded that implementation of these recommendations would offer increased benefits to women, particularly those at high risk. The GDG also expected that standards would improve and the service provided to women would be more robust and consistent across the UK, thus reducing variation in practice.

The GDG noted that although published economic evaluations had been identified since the publication of the previous guidance these were only partially applicable and had serious limitations and therefore no reliable conclusions could be drawn from this evidence. No additional economic analysis had been undertaken in this area and so the GDG agreed that the conclusions of the economic analysis presented in the previous guidance should stand.

The GDG agreed that the decision to deliver the high risk surveillance programme through the national breast screening programmes, which was recommended in the previous guidance, may result in an overall reduction in cost due to the service becoming more consistent and equitable across the country and easier to audit.

7.3 Surveillance for people with a personal history and a family history of breast cancer

Any woman with primary breast cancer is at increased risk of developing breast cancer in the remaining breast tissue compared to women with no personal history of breast cancer. Women with a family history who have breast cancer are at a much higher risk. For this reason women who develop breast cancer and have a family history may be offered a risk-reducing mastectomy. Some may not be offered this and others may choose not to have this done. For those women who have breast tissue remaining it is not clear what surveillance should be offered to them. At present all women are offered mammography annually or for at least 5 years and some for longer than this (Early and locally Advanced Breast Cancer Guideline CG80)[27]. It is known that detecting a second event at an early stage compared to a late stage does confer a survival advantage.

It is not known whether offering mammographic surveillance confers a survival advantage to those with a family history of breast cancer as well as to those who do not have a family history of breast cancer. It is not known what the optimal frequency of mammography is. It is known that MRI is more sensitive than mammography. Digital mammography is known to be more sensitive than analogue mammography for the detection of breast cancer in pre menopausal women and in women with dense breasts.

In current practice women aged 35 years at diagnosis of their first breast cancer who also have a strong family history of breast cancer are likely to be discharged from any form of surveillance when aged 40 years when they are discharged from the follow-up of their cancer, whereas their sister, who has not had breast cancer and consequently has less risk of an incident breast cancer, is eligible for surveillance at the same age.

There is currently no guidance on the most appropriate surveillance protocol for women with a personal history of breast cancer and an increased risk due to family history. Consequently practice is variable and many women are not receiving optimal care.

Clinical Question: What are the specific surveillance needs of people with a personal history of breast cancer and a familial risk, who have not undergone a risk-reducing bi-lateral-mastectomy?

Clinical Evidence (new 2013) (see also full evidence review)

Study quality and results (Diagnostic Outcomes)

Evidence about the surveillance needs of women with a personal history and familial risk of breast cancer drawn from two publications: a systematic review of eight studies (Robertson, *et al.,* 2011) and a primary study (Sardanelli, *et al.,*, 2011).

[27] CG80 Early and locally advanced breast cancer: full guideline

None of the nine studies included in Roberston, *et al.,* (2011) was considered high quality (using QUADAS criteria). The main limitations were: unclear time between index and reference tests, lack of blinding for both index and reference tests and partial verification bias. No meta-analysis was done in the review due to heterogeneity across the studies.

Sardanelli, *et al.,* (2011) included asymptomatic patients at high risk for breast cancer and who were proven *BRCA1/2* carriers or who were untested first-degree relatives of *BRCA1/2* carriers or who had a strong family history of breast or ovarian cancer and also included women with a personal history of breast cancer provided they had not undergone bilateral total mastectomy. The study did not however present the diagnostic outcomes by subgroup and therefore caution should be used when interpreting the results as they also include women with no personal history. This study was not considered high quality due to the unrepresentative spectrum of patients and lack of blinding of index and reference tests.

Both studies assessed the diagnostic performance of a number of interventions including clinical breast exam, mammography, ultrasonography, MRI as well as a number of different combinations of interventions.

Robertson, *et al.,* (2011) reported on the diagnostic performance of all surveillance methodologies for detecting ipsilateral and contralateral breast cancer separately. Diagnostic performance results were also reported separately comparing patients undergoing routine surveillance with patients undergoing non-routine surveillance where possible.

Sardanelli, *et al.,* (2011) reported diagnostic performance of the different surveillance methods for women <50 years of age compared and women ≥50 years separately where available.

Evidence Statements (Diagnostic outcomes)

Moderate quality evidence (Robertson *et al.,*, 2011) suggests that MRI has the optimal combination of sensitivity and specificity for the detection of ipsilateral breast tumour recurrence in patients undergoing routine surveillance and non-routine surveillance following breast conserving surgery.

Moderate quality evidence (Robertson, *et al.,* 2011) suggests that MRI has higher sensitivity and specificity for the detection of ipsilateral breast tumour recurrence in patients undergoing surveillance following breast conserving surgery. In this review combined surveillance mammography, clinical breast examination (CBE), ultrasound and MRI had the highest sensitivity (100%) for the detection of metachronous contralateral breast cancer in surveillance following breast conserving surgery (Robertson, *et al.,* 2011).

For patients undergoing routine surveillance following mastectomy moderate quality evidence (Roberston, *et al.,* 2011) suggests MRI has higher sensitivity than mammography or clinical examination for the detection of ipsilateral breast tumour recurrence. In these patients combined surveillance mammography and ultrasound had the highest sensitivity (95%) and specificity (99%) for the detection of metachronous contralateral breast cancer.

Moderate quality evidence from a surveillance study including women with and without a personal history of breast cancer (Sardanelli, *et al.,* 2011), suggests that MRI is more sensitive than mammography, ultrasonography, clinical breast examination or combined mammography and ultrasonography.

Moderate quality evidence, from a surveillance study including women with and without a personal history of breast cancer (Sardanelli, *et al.,* 2011), suggests no significant different in

the sensitivity of MRI + Mammography, MRI + ultrasonography, MRI + Mammography + Ultrasonography or MRI. (see table 7.6 -7.7)

Table 7.6: Sensitivities, specificities, positive likelihood ratios and negative likelihood ratios for tests and combinations of tests for both contralateral and ipsilateral breast cancer (reported as ranges).

	No of studies	Incidence Rate (screen detected and interval cancers)	Sensitivity (range)	Specificity (range)	No of Studies	+LR (range)	-LR (range)
Clinical breast examination	5* (Robertson, 2011 and Sardanelli, 2011)	3.3% (95% 2.4%-4.3%) taken from Sardanelli, 2011)	0%-89%	49%-99.3%	4	1.0-26.4	0.2-0.83
Mammography	6* (Robertson, 2011 and Sardanelli, 2011)	3.3% (95% 2.4%-4.3%) taken from Sardanelli, 2011)	50%-83%	50%-99%	6	1.3-52.3	0.3-0.7
Ultrasonography	3* (Robertson, 2011 and Sardanelli, 2011)	3.3% (95% 2.4%-4.3%) taken from Sardanelli, 2011)	43%-87%	31%-98.4%	3	0.6-33	0.2-1.8
MRI	7* (Robertson, 2011 and Sardanelli, 2011)	3.3% (95% 2.4%-4.3%) taken from Sardanelli, 2011)	86%-100%	50%-96.7%	4	1.3-27.6	0.09-0.7
Mammography+ultrasonography	2* (Robertson, 2011 and Sardanelli, 2011)	3.3% (95% 2.4%-4.3%) taken from Sardanelli, 2011)	62%-95%	97.6%-99%	2	26-61.5	0.05-0.38
MRI+mammography	1* (Sardanelli, 2011)	3.3% (95% 2.4%-4.3%) taken from Sardanelli, 2011)	93.2%	96.3%	1	25.4	0.07
MRI+ultrasonography	1* (Sardanelli, 2011)	3.3% (95% 2.4%-4.3%) taken from Sardanelli, 2011)	93.3%	96%	1	23.6	0.07
Clinical Exam + mammography	1* (Sardanelli, 2011)	3.3% (95% 2.4%-4.3%) taken from Sardanelli, 2011)	100%	67%	1	3.0	
Mammography + Clinical Exam + Ultrasound	1* (Sardanelli, 2011)	3.3% (95% 2.4%-4.3%) taken from Sardanelli, 2011)	64%	84%	1	3.9	0.4
Mammography + Clinical Exam +Ultrasound +MRI	1* (Sardanelli, 2011)	3.3% (95% 2.4%-4.3%) taken from Sardanelli, 2011)	100%	89%	1	8.9	

***Total number of individual studies from the systematic reviews which reported results for each imaging modality or combination of modalities

Table 7.7: Sensitivities, specificities, positive likelihood ratios and negative likelihood ratios for Mammography, ultrasonography and MRI by age (taken from Sardanelli, *et al.*,, 2011).

	Sensitivity (%)	Specificity (%)	+LR	-LR
Women <50 (941 rounds)				
Mammography	10/22	628/636	36.1 (13.0-100.4)	0.55 (0.27-1.13)
	45.5 (24.4-67.8)	98.7 (97.5-99.5)		
Ultrasonography	9/21	620/630	27.0 (9.9-73.4)	0.58 (0.28-1.19)
	42.9 (21.8-66.0)	98.4 (97.1-99.2)		
MRI	16/18	595/616	26.1 (11.7-58.1)	0.12 (0.03-0.50)
	88.9 (65.3-98.6)	96.6 (94.8-97.9)		
Women ≥50 (651 rounds)				
Mammography	15/28	407/409	109.6 (23.9-503.1)	0.47 (0.24-0.91)
	53.6 (33.9-72.5)	99.5 (98.2-99.9)		
Ultrasonography	17/29	380/386	37.7 (13.8-103.0)	0.42 (0.21-0.84)
	58.6 (38.9-76.5)	98.4 (96.6-99.4)		
MRI	26/28	371/383	29.6 (13.5-64.9)	0.07 (0.02-0.31)
	92.9 (76.5-99.1)	96.9 (94.6-98.4)		

Evidence Statements (Clinical Outcomes)

No evidence was found about the relative effect of surveillance MRI, mammography, ultrasound, clinical breast examination and no surveillance on stage at detection, overall survival, radiation induced cancer or health related quality of life.

Very low quality evidence (Elmore, *et al.,* 2010; table 7.8) suggests a new breast cancer will be detected on approximately 1% of surveillance tests in women with a personal history of breast cancer and a familial risk.
Low quality evidence (Houssami, *et al.,* 2011: Table 7.8) reported a cancer detection rate of 95.5/10,000 screens (95% CI, 78.3-112.7) for screening with mammography.

Although Sardanelli, *et al.,*.,(2010) reported both clinical and diagnostic outcomes, the results for clinical outcomes are reported for all interventions combined and not for individual outcomes and therefore there is a question mark over usefulness of the clinical data from this study in supporting the drafting of recommendations.

Table 7.8: GRADE Profile: What is the effectiveness of specific surveillance methodologies for people with a personal history of breast cancer and a familial risk, who have not undergone a risk-reducing mastectomy?

Quality assessment						Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	
Incidence of breast cancer recurrence[9] (follow-up 18-54 months[1]) Elmore, *et al.,* (2010)						
1	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	VERY LOW
Incidence of new breast cancer (follow-up 18-54 months[1]) Elmore, *et al.,* (2010)						
1	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	VERY LOW
Interval and screen detected cancers (follow-up 12-96 months) Sardanelli, *et al.,* (2011)						
1	observational studies	serious[4]	no serious inconsistency	serious[5]	no serious imprecision[6]	VERY LOW
Cancer Detection Rates (Houssami, *et al.,*, 2011)						
1	observational studies	serious[10]	no serious inconsistency	no serious indirectness	no serious imprecision	LOW

[1] Not clear from the study though patients are drawn from a three year period and it appears that 1st surveillance spanned and 18 month period following treatment which would give a minimum follow-up of 18 months and maximum follow-up of 54 months.
[2] This study is a retrospective study with a high risk of bias based on Review Manager assessment of study quality
[3] Small numbers included in the study over a three year period (n=141)
[4] None randomised, open label study
[5] Not all included women will have a personal history however all included women have a high risk of inherited breast cancer and the study reported a significant difference in the incidence rate per woman-year between women with a personal history of breast cancer and women without (p=0.045).
[6] N=501 patients included
[7] Unclear whether including only women with a personal history and a high risk of inherited breast cancer would change the result and if so, in which direction.
[9] Stated as an outcome yet not clearly reported
[10] Retrospective observational study, no information given on exclusion criteria and no details on follow up times

Cost effectiveness evidence for surveillance for people with a personal history of breast cancer (2013) (see also full cost effectiveness evidence review)

A literature review of published cost effectiveness analyses identified one relevant paper, (Schousboe, *et al.,* 2011). Further health economic analysis was undertaken (see full cost-effectiveness evidence) to compare the cost-effectiveness of different surveillance methods for women and men with a family history and a personal history of breast cancer who have not undergone risk-reducing mastectomy. The decision to offer certain types/frequencies of surveillance will impact on NHS resources and patient benefits and was identified as a high economic priority.

Study quality and results

One study was included for this topic. This paper was deemed partially applicable to the guideline. The reasons for partial applicability were that the analyses was conducted in the US and not the UK and did not conform to aspects of the NICE reference case. This paper was deemed to have very serious limitations. The results of this study are summarised in table 7.9.

Evidence statements

One study was included for this topic. The study (Schousboe, *et al.,* 2011) was conducted in the USA in 2011. This study showed that Biennial mammography cost less than £56,296[28] per QALY gained for women aged 40 to 79 years with both a family history of breast cancer and a previous breast biopsy, regardless of breast density. Annual mammography was not cost-effective for any group, regardless of age or breast density. The results are not applicable to carriers of *BRCA1* or *BRCA2* mutations.

[28] Converted from 2008 U.S dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 103% (http://eppi.ioe.ac.uk/costconversion/default.aspx).

Table7.9: Economic evidence profile: Cost effectiveness of surveillance for people with a personal history of breast cancer

Quality assessment			*Summary of findings*						
Study	*Limitations*	*Applicability*	*Population*	*Intervention*	*Comparator*	*Incremental cost (2011 £)*	*Incremental effects*	*ICER*	*Uncertainty*
Schousboe, 2011	Very serious limitations [1]	Partially applicable [2]	Cohort of US women aged over 40 with a family and personal history of breast cancer (secondary analysis)	Annual mammography, biannual mammography and mammography every 3 to 4 years	No mammography	Not specifically reported	Number of women screened over 10 years to prevent 1 death from breast cancer: Screening strategy: 337 Mammography every 3 to 4 years (age 70-79, BI-RADS 4): 4870 Mammography every 3 to 4 years (age 40-49, BI-RADS 2): 2041 Biannual mammography (age 60-69, BI-RADS 4): 12195 Biannual mammography (age 40-49, BI-RADS 2)	Mammography every 3 to 4 years (age 50-59, BI-RADS 1 and personal as well as family history of BC): £17,680.52[3]	Univariate sensitivity analysis and probabilistic sensitivity analysis reported. Results (ICERs) are sensitive to detection rate of false-positives, magnitude of excess DCIS detection, shift from advanced to local disease, breast cancer incidence.

[1] Quality of life data is based on one single publication of a Swedish research group; model is based on US population data and makes several assumptions due to lack of published data. Family and personal history are only considered in the secondary analysis and results are not applicable to BRCA1/2 mutation carriers. Therefore the relevance of these results for informing the current guideline is limited.

[2] The analysis does not meet one or more aspects of the NICE reference case.

[3] Converted from 2008 U.S dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 103% (http://eppi.ioe.ac.uk/costconversion/default.aspx

Health Economic Evaluation (see also full cost effectiveness evidence review)

Different surveillance methods and strategies are available to screen women with a personal history of breast cancer for contralateral and ipsilateral recurrences. The decision to offer certain types/frequencies of surveillance will impact on NHS resources and patient benefits. This cannot be answered by qualitative methods as one surveillance strategy may be more expensive but may be more effective. The GDG identified this topic as a high economic priority. A systematic review of the economic evidence was conducted, a summary of which is presented in the previous section. Only one study was identified and deemed to have very serious limitations and only partially applicable. No studies were found that directly addressed the question.

CG41 assessed the relative cost-effectiveness of annual film-screen mammography, annual MRI screening and annual combined screening in women aged 30-49 years at a familial risk of breast cancer. It was agreed by the GDG that this evaluation would be based on adapting and updating the economic model in CG41. The adaptation would include people with a personal history of breast cancer and consider the surveillance needs for different sub-groups. The topic would also be adapted and up-dated to include men if feasible. However, the paucity of evidence on men was considered a potential challenge in developing the model. It was therefore agreed by the GDG that men would be considered within the same population as women.

Aim

The aim of this economic analysis was to compare the cost-effectiveness of different surveillance methods for women and men with a family history and a personal history of breast cancer who have not undergone risk-reducing mastectomy. The following screening methods were included in the analysis:

- No screening (comparator)
- Annual mammography (digital)
- Annual MRI
- Annual combined approach (mammography plus MRI)

Subgroup analyses were conducted on the following patient groups:

- High risk patients (age 30-39 years)
- High risk patients (age 40-49 years)
- High risk patients (age 50-59 years)
- High risk patients (age 60-69 years)
- *BRCA2*-positive patients (age 30-39 years)
- *BRCA2*-positive patients (age 40-49 years)
- *BRCA2*-positive patients (age 50-59 years)
- *BRCA2*-positive patients (age 60-69 years)
- *BRCA1*-positive patients (age 30-39 years)
- *BRCA1*-positive patients (age 40-49 years)
- *BRCA1*-positive patients (age 50-59 years)
- *BRCA1*-positive patients (age 60-69 years)

Model structure

CG41 was considered an appropriate model structure for adaptation with no major structural changes required.

The CG41 model comprised a deterministic decision tree and Markov model, which aimed to model the surveillance needs of individuals with a family history but no personal history of breast cancer. The decision tree modelled the probability of an individual developing breast cancer and the conditional probability of its subsequent diagnosis, dependent on the screening strategy in use. The Markov model then followed patients over time, modelling disease progression amongst the cohort. Appropriate costs and benefits were then accumulated according to the progression of each individual until death.

The following adaptations were made:

- Change of patient population to men and women with a family history and a personal history of breast cancer
- Digital mammography was considered instead of film-screen mammography
- Age groups were extended from 30-49 to 30-69 years; modelled over 4 age groups: 30-39, 40-49, 50-59, 60-69 years
- *BRCA2*-positives (previously included as part of the high risk group for CG41) were considered as a separate patient group, in addition to *BRCA1*-postives and high risk individuals
- The moderate risk group (included in CG41) was not again considered due to lack of cost-effectiveness in previous analyses, and in favour of the specification of the three patient groups defined above
- Additional capability to apply distinct breast cancer survival rates for each of the patient groups
- Additional capability to run automated probabilistic sensitivity analysis (PSA)

A UK NHS perspective was adopted in the analysis. Health outcomes have been expressed in terms of quality-adjusted life years (QALYs). The analysis undertaken was a cost-utility analysis producing cost/QALY results expressed as incremental cost effectiveness ratios (ICERs). A life-time horizon was adopted.

Model Inputs

The cost-effectiveness model required population with clinical evidence, health related preferences (utilities) and resource use/cost data. High quality evidence was needed for all parameters. Where this was not available, consideration was given to the clinical evidence used in CG41 and the expert opinion of the GDG was used to estimate relevant parameters. All data inputs were verified and validated by the GDG before analysis was undertaken.

Clinical data

The baseline values for risk of developing an episode of recurrent breast cancer in patients with a family and personal history of breast cancer were taken from literature recommended by the GDG (Schaapveld, *et al.,* 2008, Malone, *et al.,* 2010) and converted from 5-year risk to annual probabilities. The papers were chosen after a call for evidence to the GDG and after careful consideration by the GDG of the applicability of the data presented in several papers submitted in response to this call. The benefit of early cancer detection was calculated by identification of the life expectancy for each age group based on UK general population data. Disease specific mortality was used by adapting the assumptions made in CG41 for these parameters according to the current GDG's expertise.

Radiation risk

The values for the increase in lifetime risk of breast cancer per mGy of radiation have been adopted from CG41 and expanded to incorporate the 50 to 69 years age groups.

Sensitivity/specificity of surveillance methods

The major difference between CG41 and the current model is that digital mammography has since started to replace film-screen mammography in practice and was therefore used for the model population, thus requiring appropriate sensitivity/ specificity values for this technique. Sensitivity and specificity data of all other techniques were updated according to recent literature (Houssami, *et al.,* 2011, Robertson, *et al.,* 2011, Sardanelli, *et al.,* 2011) and validated by the GDG.

Utility data

The baseline utility which describes the quality of life of an individual who is not suffering from breast cancer is assumed to be the same as the average person in the general population. An age dependent baseline utility from the Health Survey for England is applied as in CG41. The utility value for a person treated for breast cancer was taken from recent literature (Peasgood, *et al.,* 2010). Based on GDG expert opinion, the model applies a utility multiplier of 1 (no change) in the annual cycle following a false negative result. All utilities were discounted at a rate of 3.5 %.

Resource use and cost data

The analysis was undertaken from an NHS perspective and the costs considered included cost of the different surveillance methods, cost of staging as well as cost of breast cancer treatment and surgery. All unit costs, where available, were taken from the British National Formulary (BNF 63) for medications and drugs, NHS reference costs (2011) for treatments and published literature (Tosteson, *et al.,* 2008). Chemotherapy treatment was micro-costed according to GDG advice and expertise. All costs are expressed in 2011/12 GBP (£) and were discounted at a rate of 3.5 %.

Sensitivity analysis

Sensitivity analysis was undertaken to test the robustness of the results of the economic model. Probabilistic and one-way sensitivity analysis was undertaken across the following scenarios applied to each sub-group:

- Mammography versus no screening
- MRI versus no screening
- MRI+ mammography versus no screening
- MRI versus mammography
- MRI+ mammography versus mammography

Results – base case

Age group 30 to 39 years

Table 7.10 presents the total costs and total QALYs estimated over a lifetime for a cohort of 1,000 individuals under each screening strategy.

Table 7.10: Base case results for the age group 30 to 39 years

	High risk		*BRCA2*		*BRCA1*	
	Total QALYs	***Total costs***	***Total QALYs***	***Total costs***	***Total QALYs***	***Total costs***
No screening	19766.35	£2,050,154	19363.11	£2,536,313	19009.83	£2,758,506
Mammography	19916.30	£3,111,010	19625.31	£3,627,730	19290.18	£3,871,473
MRI	19998.21	£4,146,673	19767.93	£4,664,445	19442.86	£4,927,887
MRI+mammography	20000.00	£4,823,684	19772.27	£5,342,108	19447.45	£5,570,690

Table 7.11 presents the full range of ICERs calculated for various screening strategies in individuals aged 30-39 years.

Table 7.11 ICERs for comparison of different screening strategies (30-39 years)

High risk	**vs. No screening**		**ICER**
Mammography	£7,075	**vs. Mammography**	
MRI	£9,042	£12,643	**vs. MRI**
MRI+mammography	£11,871	£20,461	£379,167
BRCA2	**vs. No screening**		
Mammography	£4,162	**vs. Mammography**	
MRI	£5,257	£7,269	**vs. MRI**
MRI+ mammography	£6,857	£11,666	£156,014
BRCA1	**vs. No screening**		
Mammography	£3,970	**vs. Mammography**	
MRI	£5,010	£6,919	**vs. MRI**
MRI+ mammography	£6,426	£10,804	£140,171

The results suggest that all screening strategies are expected to be cost effective compared to no screening for this age group at a threshold of £20,000 per QALY gained. Furthermore MRI is expected to be cost effective compared to mammography at this threshold, providing the highest net monetary benefit (NMB) at £20,000. Combination MRI plus mammography is not expected to be cost effective compared to MRI or mammography alone at £20,000 per QALY gained in the high risk group. The PSA results suggest we can be fairly confident of this conclusion when accounting for possible variance in the parameter values chosen since MRI is found to provide the highest NMB in over 70% of 1,000 runs.

Tables 7.12 and 7.13 present the incremental costs and incremental QALYs (per person) for each comparison.

Table 7.12: Incremental cost for all comparisons (30-39 years)

High risk	**vs. No screening**		**Δ Cost**
Mammography	£1,061	**vs. Mammography**	
MRI	£2,097	£1,036	**vs. MRI**
MRI+ mammography	£2,774	£1,713	£677
BRCA2	**vs. No screening**		
Mammography	£1,091	**vs. Mammography**	
MRI	£2,128	£1,037	**vs. MRI**
MRI+ mammography	£2,806	£1,714	£678
BRCA1	**vs. No screening**		
Mammography	£1,113	**vs. Mammography**	
MRI	£2,169	£1,056	**vs. MRI**
MRI+ mammography	£2,812	£1,699	£643

Table7.13: Incremental QALYs for all comparisons (30-39 years)

High risk	vs. No screening		Δ QALY
Mammography	0.150	vs. Mammography	
MRI	0.232	0.082	vs. MRI
MRI+ mammography	0.234	0.084	0.002
BRCA2	vs. No screening		
Mammography	0.262	vs. Mammography	
MRI	0.405	0.143	vs. MRI
MRI+ mammography	0.409	0.147	0.004
BRCA1	vs. No screening		
Mammography	0.280	vs. Mammography	
MRI	0.433	0.153	vs. MRI
MRI+ mammography	0.438	0.157	0.005

The results were robust in all one-way sensitivity analyses. The result of the probabilistic sensitivity analysis shows that at a WTP threshold of £20,000, MRI is expected to be the most-cost effective screening strategy in the high risk groups as well as in *BRCA1* and *BRCA2* carriers, with a high probability of cost-effectiveness (High risk: 0.711, *BRCA2*: 0.798, *BRCA1*: 0.829).

Age group 40 to 49 years

Table 7.14 presents the total costs and total QALYs estimated over a lifetime for a cohort of 1,000 individuals under each screening strategy.

Table 7.14: Base case results for the age group 40 to 49 years

	High risk		*BRCA2*		*BRCA1*	
	Total QALYs	*Total costs*	*Total QALYs*	*Total costs*	*Total QALYs*	*Total costs*
No screening	17958.23	£1,771,033	17975.12	£1,560,443	17787.72	£1,716,315
Mammography	18070.10	£2,823,582	18110.24	£2,609,404	17935.24	£2,776,125
MRI	18131.14	£3,856,560	18183.37	£3,634,600	18015.18	£3,811,963
MRI+ mammography	18132.45	£4,536,122	18185.13	£4,319,839	18017.06	£4,476,184

Table 7.15 presents the full range of ICERs calculated for various screening strategies in individuals aged 40-49 years.

Table 7.15: ICERs for comparison of different screening strategies (40-49 years)

High risk	vs. No screening		ICER
Mammography	£9,409	vs. Mammography	
MRI	£12,062	£16,925	vs. MRI
MRI+ mammography	£15,871	£27,468	£516,670
BRCA2	vs. No screening		
Mammography	£7,763	vs. Mammography	
MRI	£9,960	£14,020	vs. MRI
MRI+ mammography	£13,140	£22,841	£389,187
BRCA1	vs. No screening		
Mammography	£7,184	vs. Mammography	
MRI	£9,213	£12,959	vs. MRI
MRI+ mammography	£12,034	£20,780	£353,033

The results suggest that all screening strategies are expected to be cost effective compared to no screening for this age group at a threshold of £20,000 per QALY gained. Furthermore

MRI is expected to be cost effective compared to mammography at this threshold, providing the highest net monetary benefit (NMB) at £20,000. Combination MRI plus mammography is not expected to be cost effective compared to either MRI or mammography alone at £20,000 per QALY gained. There is some uncertainty around this conclusion due to possible variance in the parameter values chosen, however MRI was found to provide the highest NMB in over 60% of 1,000 runs.

Tables 7.16 and 7.17 present the incremental costs and incremental QALYs (per person) for each comparison.

Table 7.16: Incremental cost for all comparisons (40-49 years)

High risk	**vs. No screening**		**Δ Cost**
Mammography	£1,053	**vs. Mammography**	
MRI	£2,086	£1,033	**vs. MRI**
MRI+ mammography	£2,765	£1,713	£680
BRCA2	**vs. No screening**		
Mammography	£1,049	**vs. Mammography**	
MRI	£2,074	£1,025	**vs. MRI**
MRI+ mammography	£2,759	£1,710	£685
BRCA1	**vs. No screening**		
Mammography	£1,060	**vs. Mammography**	
MRI	£2,096	£1,036	**vs. MRI**
MRI+ mammography	£2,760	£1,700	£664

Table 7.17: Incremental QALYs for all comparisons (40-49 years)

High risk	**vs. No screening**		**Δ QALY**
Mammography	0.112	**vs. Mammography**	
MRI	0.173	0.061	**vs. MRI**
MRI+ mammography	0.174	0.062	0.001
BRCA2	**vs. No screening**		
Mammography	0.135	**vs. Mammography**	
MRI	0.208	0.073	**vs. MRI**
MRI+ mammography	0.210	0.075	0.002
BRCA1	**vs. No screening**		
Mammography	0.148	**vs. Mammography**	
MRI	0.227	0.080	**vs. MRI**
MRI+ mammography	0.229	0.082	0.002

The results were robust to all one-way sensitivity analysis. The result of the probabilistic sensitivity analysis shows that at a WTP threshold of £20,000, , MRI is expected to be the most-cost effective screening strategy in the high risk group and in *BRCA1* and *BRCA2* carriers, with probabilities of being cost-effective of 0.599, 0.713 and 0.656 respectively.

Age group 50 to 59 years

Table 7.18 presents the total costs and total QALYs estimated over a lifetime for a cohort of 1,000 individuals under each screening strategy.

Table 7.18: Base case results for the age group 50 to 59 years

	High risk		*BRCA2*		*BRCA1*	
	Total QALYs	*Total costs*	*Total QALYs*	*Total costs*	*Total QALYs*	*Total costs*
No screening	15671.62	£1,547,168	15815.56	£1,038,364	15719.15	£1,147,246
Mammography	15775.89	£2,606,070	15899.33	£2,081,643	15812.24	£2,198,142
MRI	15805.87	£3,627,845	15923.51	£3,099,128	15839.10	£3,221,268
MRI+ mammography	15807.05	£4,307,940	15924.25	£3,788,335	15839.90	£3,895,894

Table 7.19 presents the full range of ICERs calculated for various screening strategies in individuals aged 50-59 years.

Table 7.19: ICERs for comparison of different screening strategies (50-59 years)

High risk	**vs. No screening**		**ICER**
Mammography	£10,155	**vs. Mammography**	
MRI	£15,498	£34,082	**vs. MRI**
MRI+ mammography	£20,384	£54,612	£574,640
BRCA2	**vs. No screening**		
Mammography	£12,453	**vs. Mammography**	
MRI	£19,090	£42,090	**vs. MRI**
MRI+ mammography	£25,300	£68,489	£925,448
BRCA1	**vs. No screening**		
Mammography	£11,290	**vs. Mammography**	
MRI	£17,292	£38,089	**vs. MRI**
MRI+ mammography	£22,763	£61,363	£836,821

The results suggest that mammography and MRI are expected to be cost effective compared to no screening for this age group at a threshold of £20,000 per QALY gained. However, MRI is not expected to be cost effective compared to mammography. Combination MRI plus mammography is not expected to be cost effective compared to any other screening strategy at a threshold of £20,000 per QALY gained. While the PSA results suggest that uncertainty surrounding the parameter values chosen could affect the conclusion regarding the most cost effective strategy, mammography provided the highest NMB in almost 60% of 1,000 PSA runs, with a further 20% provide by MRI.

Tables 7.20 and 7.21 present the incremental costs and incremental QALYs (per person) for each comparison.

Table 7.20: Incremental cost for all comparisons (50-59 years)

High risk	**vs. No screening**		**Δ Cost**
Mammography	£1,059	**vs. Mammography**	
MRI	£2,081	£1,022	**vs. MRI**
MRI+ mammography	£2,761	£1,702	£680
BRCA2	**vs. No screening**		
Mammography	£1,049	**vs. Mammography**	
MRI	£2,074	£1,025	**vs. MRI**
MRI+ mammography	£2,759	£1,710	£685
BRCA1	**vs. No screening**		
Mammography	£1,051	**vs. Mammography**	
MRI	£2,074	£1,023	**vs. MRI**
MRI+ mammography	£2,749	£1,698	£675

Table 7.21: Incremental QALYs for all comparisons (50-59 years)

High risk	vs. No screening		Δ QALY
Mammography	0.104	vs. Mammography	
MRI	0.134	0.030	vs. MRI
MRI+ mammography	0.135	0.031	0.001
BRCA2	vs. No screening		
Mammography	0.084	vs. Mammography	
MRI	0.108	0.024	vs. MRI
MRI+ mammography	0.109	0.025	0.001
BRCA1	vs. No screening		
Mammography	0.093	vs. Mammography	
MRI	0.120	0.027	vs. MRI
MRI+ mammography	0.121	0.028	0.001

The results were robust to all one-way sensitivity analysis. The result of the probabilistic sensitivity analysis shows that at a WTP threshold of £20,000, mammography is expected to be the most-cost effective screening strategy in the high risk group and in *BRCA* 1 and *BRCA* 2 carriers, with probabilities of being cost-effective of 0.577, 0.584 and 0.536 respectively.

Age group 60 to 69 years

Table 7.22 presents the total costs and total QALYs estimated over a lifetime for a cohort of 1,000 individuals under each screening strategy.

Table 7.22: Base case results for the age group 60 to 69 years

	High risk		*BRCA2*		*BRCA1*	
	Total QALYs	*Total costs*	*Total QALYs*	*Total costs*	*Total QALYs*	*Total costs*
No screening	12927.34	£1,274,262	13053.01	£726,734	13011.02	£796,532
Mammography	13012.78	£2,330,289	13105.78	£1,762,911	13065.59	£1,835,740
MRI	13027.43	£3,350,394	13114.78	£2,785,982	13074.89	£2,860,793
MRI+ mammography	13028.91	£4,025,952	13115.69	£3,469,556	13075.82	£3,538,269

Table 7.23 presents the full range of ICERs calculated for various screening strategies in individuals aged 60-69 years.

Table 7.23: ICERs for comparison of different screening strategies (60-69 years)

High risk	vs. No screening		ICER
Mammography	£12,359	vs. Mammography	
MRI	£20,742	£69,641	vs. MRI
MRI+ mammography	£27,092	£105,150	£457,079
BRCA2	vs. No screening		
Mammography	£19,637	vs. Mammography	
MRI	£33,340	£113,698	vs. MRI
MRI+ mammography	£43,765	£172,297	£753,553
BRCA1	vs. No screening		
Mammography	£19,044	vs. Mammography	
MRI	£32,322	£110,274	vs. MRI
MRI+ mammography	£42,309	£166,390	£723,293

The results suggest that mammography is expected to be cost effective compared to no screening for this age group at a threshold of £20,000 per QALY gained. MRI and combination MRI plus mammography are expected to be cost effective compared to no

screening at a threshold of £30,000 per QALY gained in the high risk group. Neither MRI alone or combination MRI plus mammography are expected to be cost effective compared to mammography alone.

The PSA results suggest we can be fairly confident of this conclusion when accounting for possible variance in the parameter values chosen since mammography is found to provide the highest NMB over 72% of 1,000 runs.

Tables 7.24 and 7.25 present the incremental costs and incremental QALYs (per person) for each comparison.

Table 7.24: Incremental cost for all comparisons (60-69 years)

High risk	**vs. No screening**		**Δ Cost**
Mammography	£1,056	**vs. Mammography**	
MRI	£2,076	£1,020	**vs. MRI**
MRI+ mammography	£2,752	£1,696	£676
BRCA2	**vs. No screening**		
Mammography	£1,036	**vs. Mammography**	
MRI	£2,059	£1,023	**vs. MRI**
MRI+ mammography	£2,743	£1,707	£684
BRCA1	**vs. No screening**		
Mammography	£1,039	**vs. Mammography**	
MRI	£2,064	£1,025	**vs. MRI**
MRI+ mammography	£2,742	£1,703	£677

Table 7.25: Incremental QALYs for all comparisons (60-69 years)

High risk	**vs. No screening**		**Δ QALY**
Mammography	0.085	**vs. Mammography**	
MRI	0.100	0.015	**vs. MRI**
MRI+ mammography	0.102	0.016	0.001
BRCA2	**vs. No screening**		
Mammography	0.053	**vs. Mammography**	
MRI	0.062	0.009	**vs. MRI**
MRI+ mammography	0.063	0.010	0.001
BRCA1	**vs. No screening**		
Mammography	0.055	**vs. Mammography**	
MRI	0.064	0.009	**vs. MRI**
MRI+ mammography	0.065	0.010	0.001

The results were robust to all one-way sensitivity analyses. The result of the probabilistic sensitivity analysis shows that at a WTP threshold of £20,000, mammography is expected to be the most-cost effective screening strategy in the high risk group and in *BRCA1* and *BRCA2* carriers with a probability of it being cost-effective is of 0.716, 0.584 and 0.536 respectively.

Summary of results

The aim of this economic evaluation was to assess the cost-effectiveness of different screening strategies for breast cancer in patients with a previous history of breast cancer.

All results appear to be robust to changes in the key parameters in both one-way and probabilistic sensitivity analyses. Results are summarised for the three subgroups below for a NICE Willingness to pay threshold of £20,000.

High-risk group (non-carrier)

- For high-risk patients with a primary breast cancer between the ages of 30 and 49, MRI is the most cost-effective screening strategy
- For high-risk patients with a primary breast cancer between the ages of 50 and 69, mammography is the most cost-effective screening strategy

***BRCA2* group**

- For *BRCA2*-positive patients with a primary breast cancer between the ages of 30 and 49, MRI is the most cost-effective screening strategy
- For *BRCA2*-positive patients with a primary breast cancer between the ages of 50 and 69, mammography is the most cost-effective screening strategy

***BRCA1* group**

- For *BRCA1*-positive patients with a primary breast cancer between the ages of 30 and 49, MRI is the most cost-effective screening strategy
- For *BRCA1*-positive patients with a primary breast cancer between the ages of 50 and 69, mammography is the most cost-effective screening strategy

Recommendations

- Offer annual MRI surveillance to all women aged 30–49 years with a personal history of breast cancer who are at high risk of contralateral breast cancer or have a *BRCA1* or *BRCA2* mutation. **[new 2013]**
- Offer annual mammographic surveillance to all women aged 50–69 years with a personal history of breast cancer who are at high risk of contralateral breast cancer or have a *BRCA1 or BRCA2* mutation. **[new 2013]**
- 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[29]. **[new 2013]**
- Before decisions on surveillance are made, discuss and give written information on the risks and benefits of surveillance, including:
  - the possible reduced sensitivity of mammography in younger women with dense breasts and the increased likelihood of further investigations
  - possible over diagnosis
  - the risk associated with exposure to radiation
  - the possible psychological impact of a recall visit. **[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]**
- 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. **[new 2013]**
- Ensure that women know the reasons for any changes to the surveillance plan**. [new**

[29] 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)

2013]

- For women under 50 years who are having mammography, use digital mammography at centres providing digital mammography to national breast screening programme standards. **[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]**
- Ensure that MRI surveillance includes MRI of both breasts performed to national breast screening programme standards. **[new 2013]**
- 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 MRI surveillance. (An example of an acceptable method is BOADICEA) **[new 2013]**
- Do not offer surveillance to women who have undergone a bilateral mastectomy**. [new 2013]**

Linking evidence to recommendations

The aim of this topic was to determine the specific surveillance needs of women with a personal history and a family history of breast cancer, who have chosen not to undergo a risk-reducing mastectomy. The GDG examined the specific surveillance needs using evidence of both the diagnostic accuracy of surveillance methods and the clinical outcomes of individual surveillance methods.

The GDG considered sensitivity, specificity, positive predictive value and negative predictive value in a range of different age groups to be the most relevant outcomes for diagnostic accuracy. The GDG considered stage at detection, overall survival, incidence of breast cancer, incidence of radiation-induced cancer, interval cancers and health related quality of life to be the most important clinical outcomes.

Diagnostic accuracy outcomes were reported including sensitivity and specificity. For the clinical outcomes only incidence of breast cancer and interval cancers were reported.

GRADE methodology was used to assess the quality of studies included within the clinical outcomes analysis. The quality of this evidence was very low for all outcomes on GRADE assessment. For diagnostic outcomes, QUADAS assessment was used in the systematic reviews to assess the quality of the included studies and none of the studies were considered to be of high quality on assessment by the review authors.

The GDG noted from the base case results of the health economic analysis, that MRI emerged as the most cost effective surveillance technique in the 30-39 and 40-49 age groups at a willingness to pay threshold of £20,000/QALY. Probabilistic sensitivity analysis confirmed that these results were robust for both the high-risk group and BRCA1 and BRCA2 carriers.

The GDG agreed that the potential benefits of annual surveillance with MRI in women aged 30-49 included diagnosing breast cancer at an earlier stage, which would help to reduce

mortality from a second primary cancer or recurrence. The GDG also noted that the costs of treatment were likely to be reduced for cancers which are caught earlier and that patient quality of life is likely to be improved with earlier detection.

The GDG acknowledged that there was more chance of a false positive recall when using MRI however they felt that when weighed against the potential survival benefits from performing MRI, it was not enough to prevent them from recommending MRI surveillance for this group of women.
Based on this information, the GDG decided to recommend annual MRI surveillance for all women aged 30-49 years who were at high risk of future breast cancer or who carried a BRCA1 or BRCA2 mutation.

The GDG also noted from the base case results of the health economic analysis that mammography emerged as the most cost effective surveillance technique in the 50-59 and 60-69 age groups, at a willingness to pay threshold of £20,000/QALY. Probabilistic sensitivity analysis confirmed that these results were robust for both the high-risk group and BRCA1 and BRCA2 carriers.

The GDG discussed whether it would be appropriate to recommend MRI for women over 50, based on the results of the health economic analysis. The GDG noted that the analysis had shown that MRI was not cost effective when compared with mammography, even at a higher willingness to pay threshold of £30,000/QALY. Consequently there was GDG consensus that MRI could not be recommended for women over 50.

The GDG agreed that recommending annual mammography in women aged 50-69 would probably result in fewer interval cancers and a likely overall survival advantage when compared with the current 3 yearly mammography surveillance. They also noted that the use of annual mammography would probably result in earlier detection of recurrences in the breast affected with the original primary.

Therefore the GDG decided to recommend annual mammography surveillance for all women aged 50-69 years who were at high risk of future breast cancer or who carried a BRCA1 or BRCA2 mutation.

The GDG agreed, based on their clinical and patient experience, that providing information on surveillance to women with a personal history and a family history of breast cancer would enable women to make an informed choice and probably improve quality of life. The GDG noted that the recommendations in the previous guidance on information provision on surveillance were also relevant to this group of women and decided to adopt them.

The GDG noted that there was a lack of data comparing surveillance with MRI and surveillance with mammography in women over 50 with a personal and family history of breast cancer. They therefore recommended further research in this area to establish the risks and benefits of these two surveillance techniques.

The GDG also acknowledged that whilst they believe there is a survival advantage from diagnosing breast cancer at an earlier stage, the evidence to support this is limited. They therefore recommended further research to access the benefit of MRI surveillance in terms of mortality of all ages for people with a personal history of breast cancer.

Research Recommendation

- Research is recommended to establish the risk and benefits of MRI surveillance compared with mammography in women over 50 years with a personal history of breast cancer. Studies should include sub-analysis for breast density.**[new 2013]**
- Research is recommended to access the benefit of MRI surveillance in terms of mortality of all ages for people with a personal history of breast cancer.**[new 2013]**

7.3.1 Women with breast cancer and a family history

For women at moderate risk of a further breast cancer the GDG felt that surveillance needs to be consistent with the recommendations that have already been produced as part of the early breast cancer guidelines (CG80).

Recommendations

Healthcare professionals involved in surveillance for people with a personal and family history of breast cancer should ensure that surveillance is line with 'Early and locally advanced breast cancer' (NICE clinical guideline 80) and in particular the following two recommendations:

- Offer annual mammography to all patients with early breast cancer, including DCIS[30], until they enter the NHSBSP/BTWSP[31]. Patients diagnosed with early breast cancer who are already eligible for screening should have annual mammography for 5 years. **[2009]**
- On reaching the NHSBSP/BTWSP screening age or after 5 years of annual mammography follow-up we recommend the NHSBSP/BTWSP stratify screening frequency in line with patient risk category. **[2009]**

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8 Risk reduction and treatment strategies

The objectives of this chapter are to describe the risk factors and treatment strategies that are relevant for women at an increased risk of breast cancer due to their family history. The chapter covers:

- the effects of lifestyle modification in respect of:
  - Menstrual and reproductive factors
  - Reproduction and fertility issues
  - Exogenous hormone treatment (contraceptives and hormone replacement therapy)
  - Breastfeeding
  - Alcohol consumption
  - Smoking
  - Weight and physical activity

- The treatment strategies that may be employed:
  - Chemoprevention
  - Risk-reducing surgery (breast or ovarian)
  - Hormone replacement therapy
  - Treatment of people with breast cancer who carry a *TP53* mutation

8.1 Risk Factors

Most cancers do not have a single cause; they result from the interaction of multiple factors that range from genetic characteristics to personal lifestyle. The term risk factor refers to anything that is associated with an increased chance of developing a particular type of cancer. Risk factors are a matter of probability. They influence an individual's odds of developing a disease. That is not the same thing as actually causing a disease to occur. Some people with one or more risk factors for a particular type of cancer never develop it, while other people who have no known risk factors do develop that type of cancer. Most breast cancer cases fall into the second category, because they are not predicted by known risk factors. Nevertheless, identification of risk factors for cancer can be useful for risk modification or to identify individuals who may benefit more from cancer screening.

Traditionally, scientists divided the factors that influence an individual's odds of developing a disease into two groups: modifiable risk factors and non-modifiable risk factors (also called predisposing factors or predispositions). Modifiable risk factors are aspects of an individual's lifestyle that affect the risk of a disease that can be altered, such as diet or smoking.

Health education efforts have usually focused on modifiable risk factors because they can be altered or eliminated. Non-modifiable risk factors (or predisposing factors) are inherent; for example, age, or aspects of an individual's genetic makeup such as sex or specific gene mutations that increase that person's likelihood of developing a disease.

For women as a whole, incidence of breast cancer increases with age. The risk of breast cancer is higher in middle-aged and elderly women than in young women. Other possible risk factors are considered in more detail in this section.

8.1.1 Risks associated with a family history

The risk of breast cancer in women with an affected first-degree relative (mother, sister or daughter) is approximately twice the risk to other women. The risk of breast cancer is related to the strength of the family history. The risk increases with the number of affected relatives, and increases as the age of affected relative(s) decrease. Only a minority of this increase in risk is due to the known high risk genes *BRCA1*, *BRCA2* or *TP53*. The chance of carrying a gene mutation is related to the strength of the family history not only of breast cancer but also of ovarian cancer, pancreatic, prostate and male breast cancer.

Some risk factors cannot be changed, e.g. age or sex. Some others are often difficult to change as actions or behaviours have already taken place that affect risk, such as the age at which a woman has children. Other risk factors are more amenable to influence and change such as diet and exercise behaviour. Different types of risk factors are discussed to allow an overall profile to be developed for individual women.

Recommendations

- People should be provided with standardised written information about risk, including age as a risk factor (see box 1). **[2004]**
- Modifiable risk factors should be discussed on an individual basis in the relevant care setting. **[2004]**

8.1.2 Menstrual and reproductive factors

Women who reach menarche (the first menstrual period) at a relatively early age and those who reach menopause at a relatively late age are more likely than other women to develop breast cancer. Nulliparity and late age at first birth both increase lifetime risk of breast cancer.

Previous studies have raised the issue of a potential increased risk of ovarian and possibly breast cancer associated with induced ovulation in sub-fertile women.

Clinical Evidence (2004) (see also full evidence review)

Meta-analysis evidence regarding the effect of menstrual and reproductive factors on breast cancer risk is of varying quality, covers different time periods, and relates to specific populations of women, namely from the Italian and Japanese populations.

Bearing in mind these differences between studies, some trends, however, have been identified from the main findings.

Age at menarche

Both studies observed an increased breast cancer risk associated with younger age at onset of menstruation. Significant increases of 32% and 19% in women aged 12-14 years and less than 12 years at menarche, respectively, compared to women aged 15 year or over at menarche were found in the earlier study (Negri, *et al.,* 1988). Conversely, in the second study (Nagata, *et al.,* 1995), onset of menstruation at age 16 or over was found to be significantly associated with a 32% decrease in breast cancer risk, relative to women aged less than 14 years at menarche.

Age at 1st (live) birth

Older age at 1st live birth (Negri, *et al.,*) or at 1st birth (Nagata, *et al.,* 1995) was associated with significant increases in breast cancer risk in both studies. In the first of the studies, women aged between 22-24 years, 25-27 years and 28 years or over had increases in risk of 22%, 40% and 75%, respectively, relative to women aged less than 22 years (Negri, *et al.,* 1988). In the second study, women aged between 25-29 years, 30-34 years and 35 years or more had odds rations of 1.32, 1.71 and 2.26, relative to women aged under 24 years and younger years (Nagata, *et al.,* 1995).

Parity

In both studies increased parity was found to be associated with a decrease in breast cancer risk, with significant decreases in risk of 38% in women who reported 5 or more live births (Negri, *et al.,* 1988), and 32% in women who reported 3 or more births (Nagata, *et al.,* 1995), compared to women who reported one birth.

Menopausal status

In the first of the studies (Negri, *et al.,* 1988), women who experienced an earlier menopause (aged between 45-49 and less than 45 years) had a 23% and a 27% decrease, respectively, in breast cancer risk, relative to women who were aged 50 years or over at menopause. In the second study (Nagata, *et al.,* 1995), no increased breast cancer risk was observed in women aged 50 or more at menopause compared to women aged under 50 years. However, premenopausal women were found to have a 2-fold increase in breast cancer risk relative to women aged under 50 years at menopause.

Women with a family history

The Collaborative reanalysis found that the relationships between risk factors for women with a family history were similar to those for women without a family history.

Induced Abortion

One meta-analysis has been identified from the literature which evaluates the association between induced abortion and breast cancer risk in the female population in general. No studies have been identified which evaluate a relationship between induced abortion and breast cancer risk in women with a family history of breast cancer.

Sub-fertility and induced ovulation

One systematic review looked at the issue of sub-fertility and induced ovulation (by use of fertility drugs). One study looked at incidence of cancer following fertility treatment in a UK clinic

Evidence Statements (2004)

Older age at 1st live birth, or at 1st birth, is associated with significant increases in breast cancer risk. (III)

Increased parity has been found to be associated with a decrease in breast cancer risk;

- 38% decrease in risk in women who reported 5 or more live births
- 32% decrease in risk in women who reported 3 or more births compared to women who reported 1 birth (III)

Earlier menarche is associated with an increase in risk of breast cancer. (III)

For women with a family history, the relative risk of menstrual and reproductive factors is consistent with the population. (III)

Recommendation

- Healthcare professionals should be able to provide information on the effects of hormonal and reproductive factors on breast cancer risk. **[2004]**

8.1.4 Hormonal contraceptives

Numerous scientific studies have investigated the relationship between the use of oral contraceptives (birth control pills) and the risk of breast cancer. In considering any increase in breast cancer risk, one has to recognise the addition of exogenous oestrogen but it may be that at least part of the effect is due to the fact that the oral contraceptive pill does prevent women from becoming pregnant, thereby reducing the breast cancer protection of an early pregnancy**.**

Clinical Evidence (2004) (see also full evidence review)

The above evidence regarding the use of oral contraceptives and their impact on breast cancer risk is of varying quality, covers different time periods, and relates to slightly different populations and outcomes. Key elements of the individual studies in these respects are summarised in the full evidence review. Of the meta-analyses/re-analysis, four (Romieu, *et al.,* 1990, Delgado-Rodriguez, *et al.,* 1991, Hawley, *et al.,* 1995, Collaborative Group, 1996) combine evidence from approximately the same time periods, with some form of quality assessment of included studies undertaken in two of the syntheses. Of the remaining two meta-analyses (Rushton, *et al.,* 1992, Schlesselman, 1995), both combine evidence published after 1980, with no quality assessment of included studies in either synthesis.

Bearing in mind these differences between studies, some trends, however, have been identified from the main findings.

Ever-use of oral contraceptives

Findings of 2 meta-analyses and the 2 recent case-control studies suggest that ever-use of OCs in all women is not associated with an increased risk of breast cancer (Romieu, *et al.,* 1990, Hawley, *et al.,* 1995, van Hoften, *et al.,* 2000, Marchbanks, *et al.,* 2002). The re-analysis found, however, that ever-use of OCs in all women was associated with a statistically significant 7% increase in breast cancer risk (Collaborative Group, 1996). A further meta-analysis similarly found a 7% increase in risk of breast cancer when case-control studies where combined, but no association when cohort studies were combined (Delgado-Rodriguez, *et al.,* 1991).

In 3 meta-analyses and one case-control study, no association between ever-use of OCs in postmenopausal women and increased breast cancer risk was observed (Romieu, *et al.,* 1990, Delgado-Rodriguez, *et al.,* 1991, Rushton, *et al.,* 1992, van Hoften, *et al.,* 2000).

Findings relating to ever-use of OCs in premenopausal women, however, were inconsistent, with no association with increased risk of breast cancer observed in one of the case-control studies (van Hoften, *et al.,* 2000), but a 14% and 16% increased risk observed in 2 meta-analyses (Delgado-Rodriguez, *et al.,* 1991, Rushton, *et al.,* 1992, respectively).

Current use of oral contraceptives

Two studies which assessed the impact of current use of OCs on risk of breast cancer in all women produced different findings, with a statistically significant 24% increase in breast cancer risk observed in the re-analysis (Collaborative Group 1996), but no increase observed in one of the case-control studies (Marchbanks, *et al.,* 2002).

Duration of oral contraceptives

Increasing duration of OC use in all women was not found to be associated with an increased risk of breast cancer in 2 meta-analyses (Romieu, *et al.,* 1990, Hawley, *et al.,* 1995) and the 2 case-control studies (van Hoften, *et al.,* 2000, Marchbanks, *et al.,* 2002). In a further meta-analysis, however, increasing duration of OC use in all women was found to be associated with increased risk, with a 27% increase observed for more than 8 years of OC use (Rushton, *et al.,* 1992).

Findings relating to increasing duration of OC use and risk of breast cancer in premenopausal and postmenopausal women were also inconsistent between studies. A 46% increased risk of breast cancer after 10 years of OC use in premenopausal women was observed in one meta-analysis (Romieu, *et al.,* 1990), whereas duration of OC use of more than 10 years in premenopausal women was not found to be associated with increased risk in a case-control study (van Hoften, *et al.,* 2000). Similarly, increasing duration of OC use in postmenopausal women was not found to be associated with increased risk in one meta-analysis (Schlesselman, 1995.,), although duration of OC use of more than 10 years was associated with a statistically significant doubling in breast cancer risk in a case-control study (van Hoften, *et al.,* 2000).

Cessation of oral contraceptive use

In the re-analysis which assessed breast cancer risk in all women after stopping OC use, a 16% increased risk was observed between 1-4 years after stopping OC use, and a 7% increase between 5-9 years after stopping use (Collaborative Group, 1996). In the same study, no increased risk of breast cancer in all women was observed 10 or more years after they stopped OC use. In a case-control study, however, no increase in risk of breast cancer was observed in all women relating to time since they stopped OC use (Marchbanks, *et al.,* 2002).

Oral contraceptive use before 1st full-term pregnancy

Statistically significant increases in risk of breast cancer in women who used OCs before their 1st full-term pregnancy was observed in 3 meta-analyses (Romieu, *et al.,* 1990, Delgado-Rodriguez, *et al.,* 1991, Hawley, *et al.,* 1995). In one of the meta-analyses (Romieu, *et al.,* 1990), a 72% increased risk for 4 or more years' OC use was found in this subgroup of women.

Oral contraceptive use in women with a family history of breast cancer

There was consistent evidence that the effects of OC use on breast cancer risk was similar in women with and without a family history (Romieu, *et al.,* 1990, Delgado-Rodriguez, *et al.,* 1991, Collaborative Group, 1996, Marchbanks, *et al.,* 2002).

Oral contraceptive use in women with a mutation in the BRCA1 or BRCA2 gene

There is evidence from one case-control study that ever use of OCs was associated with a 20% increase in breast cancer risk in women who were *BRCA1* mutation carriers, although *BRCA2* mutation carriers were not found to be at increased risk (Narod, et al.,2002).

Evidence Statements (2004)

Use of oral contraceptives slightly increases the risk of breast cancer. (III)

This increase in risk appears to be confined to current and recent use (within 5-10 years, relative risk 1.24 for current users). (III)

In women with a positive family history, the relative risk is consistent with findings in the general population. (III)

One study has shown an increased risk for *BRCA1* mutation carriers (odds ratio 1.20, relative risk under 40 = 1.40). (III)

There is no evidence regarding the progesterone only contraceptives and risk associated with family history.

Recommendations

- Advice to women up to age 35 years with a family history of breast cancer should be in keeping with general health advice on the use of the oral contraceptive pill. **[2004]**
- Women aged over 35 years with a family history of breast cancer should be informed of an increased risk of breast cancer associated with taking the oral contraceptive pill, given that their absolute risk increases with age. **[2004]**
- For women with *BRCA1* mutations, the conflicting effects of a potential increased risk of breast cancer under the age of 40 years and the lifetime protection against ovarian cancer risk from taking the oral contraceptive pill should be discussed. **[2004]**
- Women should not be prescribed the oral contraceptive pill purely for prevention of cancer, although in some situations reduction in ovarian cancer risk may outweigh any increase in risk of breast cancer. **[2004]**
- If a woman has a *BRCA1* mutation and is considering a risk-reducing oophorectomy before the age of 40 years, the oral contraceptive pill should not be prescribed purely for the reduction in ovarian cancer risk. **[2004]**

8.1.5 Breastfeeding

If breast-feeding does protect against breast cancer, it may do so by delaying the resumption of ovulation (with its accompanying high oestrogen levels) after pregnancy. The benefits of breast-feeding for the infant are well established, and all authorities agree that breast-feeding is the preferred method of infant feeding unless it is contraindicated for a specific medical reason.

Clinical Evidence (2004) (see also full evidence review)

Results of one systematic review, 1 meta-analysis and 1 collaborative re-analysis conclusively found a significant protective effect of breastfeeding on breast cancer risk. For the systematic review, the evidence was suggestive of a slight decrease in risk limited to premenopausal women, especially women from non-Western countries with long durations of breastfeeding. The meta-analysis found a significant reduction of 16% in breast cancer risk associated with ever breastfeeding compared to never breastfeeding, which was more marked in women who were non-menopausal at the time of breast cancer diagnosis. A significant trend towards decreasing risk with increasing duration of breastfeeding was also observed, with a 28% reduction in breast cancer risk in women who breastfed for at least 12

months. In the collaborative re-analysis, similarly, breast cancer risk was significantly reduced by 4.3% for each year of breastfeeding, in addition to a reduction in risk associated with each birth. For women with a family history of breast cancer, similar risk reductions were observed.

Evidence Statement (2004)

Breastfeeding confers a protective effect on breast cancer risk. (III)

The protective effect of breast feeding is in addition to the protective effect of pregnancy alone. (III)

The reduction in breast cancer risk is related to total duration of breast feeding. (III)

The Collaborative Group found that each twelve months of breastfeeding confers a reduction of about 4%. (III)

The relative risk reduction is similar in women with a family history. (III)

Recommendation

- Women should be advised to breast feed if possible because this is likely to reduce their risk of breast cancer, and is in accordance with general health advice. **[2004]**

8.1.6 Hormone replacement therapy

Factors that influence the amount of oestrogen produced by a woman's body over her lifetime (such as the ages at the onset of menstruation and at menopause) are known to influence breast cancer risk. Possible effects on breast cancer risk are only one of the many factors that need to be considered by a woman and her physician when making decisions about HRT.

Clinical Evidence (2004)

The evidence regarding the use of HRT and its impact on breast cancer risk is of varying quality, relating to slightly different populations and outcomes. Key elements of the individual studies in these respects are summarised in the full evidence review. The 4 meta-analyses (Dupont, *et al.,* 1991; Steinberg, *et al.,* 1991; Sillero-Arenas, *et al.,* 1992; Colditz, *et al.,* 1993) combine evidence from approximately the same time periods and databases, with some form of quality assessment of included studies undertaken in 3 of the syntheses. The re-analysis (Collaborative Group, 1997) includes more recent studies, although quality assessment of included studies does not appear to have been systematically undertaken. Included studies in the qualitative review (Bush, *et al.,* 2001), which has the most comprehensive coverage of all the syntheses, have also not undergone quality assessment. The Million Women Study presented results from over a million women in the UK, of whom 50% were ever users of HRT. The main analyses were concerned with breast cancer risk.

Bearing in mind these differences between studies, some trends, however, have been identified from the main findings of these meta-analyses/reviews.

Ever-use of HRT

Ever-use of HRT in postmenopausal women was associated with a statistically significant increase in relative risk of breast cancer of 1.43 in the Million Women Study and 1.06 and

1.14 in two of the other studies (Sillero-Arenas, *et al.,* 1992; Collaborative Group, 1997, respectively). However, in a third study (Colditz, *et al.,* 1993), ever-use of HRT in postmenopausal women was not associated with an increase in breast cancer risk.

Duration of HRT use

The Million Women Study found that for current users of each type of HRT, breast cancer increased with total duration of use. Three studies found that breast cancer risk in postmenopausal women increased in relation to increasing duration of HRT use, by 30% after 15 years (Steinberg, *et al.,* 1991), 63% after 12 years (Sillero-Arenas, *et al.,* 1992) and 35% after 5 or more years (Collaborative Group, 1997). A further study (Colditz, *et al.,* 1993) found that breast cancer risk increased by 20% after more than 10 years of HRT use, and by 30% after more than 15 years of use, although some studies included premenopausal women. The 2 remaining identified studies (Dupont, *et al.,* 1991; Bush, *et al.,* 2001) both found inconsistencies in study results and were thus unable to confirm an association between duration of HRT use and breast cancer risk.

Cessation of HRT use

The Million Women Study found that the increased risk of breast cancer associated with HRT use begins to decline when HRT is stopped and reaches the same level as women who have never taken HRT after about 5 years. One study (Collaborative Group, 1997) found that the increased risk of breast cancer associated with HRT use reduces after HRT is stopped and has disappeared after about 5 years' cessation of use.

HRT use and breast cancer mortality

The Million Women Study found that the relative risk of death from breast cancer was raised in women who were current users of HRT (RR=1.22), but not in past users (RR=1.05) compared with never users of HRT. One study (Bush, *et al.,* 2001) found a significant association between HRT use and a reduction in death from breast cancer, with risk estimates of less than 1.0.

HRT use in women with a family history of breast cancer

The Million Women Study examined some of their results in a way to see what if any impact some factors, including family history, had. Family history did not have an impact on the relative risks examined (only BMI had a modifying impact on the relative risks examined). Other identified studies which assessed breast cancer risk of HRT use in relation to women with a family history of breast cancer (Steinberg, *et al.,* 1991; Colditz, *et al.,* 1993; Collaborative Group ,1997), findings were inconsistent. In one study (Collaborative Group, 1997), patterns of increased breast cancer risk associated with ever-use, current/recent use and long-term use of HRT were found for women with a family history of breast cancer which matched the study's findings for postmenopausal women in general; and in a second study (Steinberg, *et al.,* 1991), ever-use of ERT was associated with increased breast cancer risk in all women with a family history of breast cancer compared to women with no history (RR=3.4 compared to RR=1.5). However, in the third study (Colditz, *et al.,* 1993), no significant association was found between breast cancer risk and HRT use in women with a family history of breast cancer.

Evidence Statements (2004)

The totality of the evidence suggests that HRT is associated with an increase in breast cancer risk. (III)

The risk associated with HRT is small for short duration use (up to 2 years) but is in the region of a two fold risk for women taking combined HRT for 10 years or more. (III)

The benefits of early menopause on the relative risk of breast cancer are unlikely to be completely removed by taking HRT until about 50 years of age. (IV)

The Million Women Study found that the relative risk of breast cancer in current users increased with increasing total duration of use of HRT. (III)

The Collaborative Group found that risk appears to be confined to current users and women who have used HRT in the last 5 years. (III)

The Million Women Study suggests that there is little or no overall increase in the relative risk of breast cancer in past users of HRT. (III)

The Collaborative Group found that risk of HRT use disappears 5 years after stopping. (III)

The Collaborative Group has shown that there is 2.3% increase in relative risk for every year used. (III)

In women with a positive family history, the relative risk is consistent with findings in the general population. (III)

The Million Women Study found that the associated risk was substantially greater for oestrogen-progestogen than for other types of HRT. (III)

Recommendations

- Women with a family history of breast cancer who are considering taking, or already taking, HRT should be informed of the increase in breast cancer risk with type and duration of HRT. **[2004]**
- Advice to individual women on the use of HRT should vary according to the individual clinical circumstances (such as asymptomatic menopausal symptoms, age, severity of menopausal symptoms, or osteoporosis). **[2004]**
- HRT usage in a woman at familial risk should be restricted to as short a duration and as low a dose as possible. Oestrogen-only HRT should be prescribed where possible. **[2004]**
- A woman having an early (natural or artificial) menopause should be informed of the risks and benefits of HRT, but generally HRT usage should be confined to women younger than age 50 years if at moderate or high risk. **[2004]** (see also section 8.3.3)
- Alternatives to HRT should be considered for specific symptoms such as osteoporosis or menopausal symptoms. **[2004]** (see also section 8.3.3)
- Consideration should be given to the type of HRT if it is being considered for use in conjunction with risk-reducing gynaecological surgery. **[2004]**

8.1.7 Alcohol consumption

People who drink moderate amounts of alcohol have been found to have a slightly higher risk of breast cancer than do those who abstain. The mechanism for this associated risk is unclear. It may be a direct cause-and-effect relationship or due to other factors—such as differences between the lifestyles of drinkers and abstainers. The use of alcohol may vary among people who differ with regard to other factors that are known to influence breast cancer risk—such as age, obesity, and reproductive history.

Clinical evidence (2004) (see also full evidence review)

Results of 4 meta-analyses identified from the literature, which evaluate the impact of alcohol consumption on breast cancer risk in women, consistently show statistically significant increases in relative risks. Associations vary slightly between studies in terms of specific intake of alcohol and increase in breast cancer risk, with definitions of an alcoholic drink in relation to equivalent gram weight showing slight differences between studies.

One study (Longnecker, *et al.,* 1988) observed significant increases in risk with an alcohol intake of 24 g (defined as about 2 drinks) per day, although only weak or modest associations at lower levels of alcohol consumption. A subsequent study by Longnecker, (1994), however, found significantly increased relative risks of breast cancer associated with an intake of 1, 2 or 3 drinks per day (1 drink defined as 13 g of alcohol), showing strong evidence of a dose-response relationship.

The third identified meta-analysis (Smith-Warner, *et al.,* 1998) found significantly increased breast cancer risks in women who drank 30-60 g (defined as about 2-5 drinks) per day, although no increased risks were observed in women who drank 60 g or more per day compared with non-drinkers. Other breast cancer risk factors, including family history of breast cancer, did not influence these results. The fourth and most recent meta-analysis (Ellison, *et al.,* 2001) found a significant linear increase in breast cancer risk with increasing intake of alcohol of 6, 12 and 24 g (defined as about one-half, 1 and 2 drinks, respectively) per day.

Results of a systematic review (Steinberg, *et al.,* 1991) found inconsistencies in results across studies, with the authors unable to support a causal association between alcohol intake and breast cancer risk.

Results of the collaborative reanalysis of worldwide data (Collaborative Group, 2002) found that the lifetime risk of breast cancer is estimated to increase by about 0.7 per 100 women for each extra unit of alcohol consumed daily, although this increase should be considered in the context of the beneficial effects of a moderate intake of alcohol. Smoking has little or no independent effect on breast cancer risk.

A cohort study (Vachon, *et al.,* 2001) which evaluated the association between alcohol consumption and breast cancer risk in women with a family history of breast cancer compared to those who married in to these families found significantly increased risks in 1st-degree relatives of breast cancer patients who drank daily compared to non-drinkers, but non-significant increases for 2nd-degree relatives. For women who married in to these families and reported daily intake of alcohol, no significantly increased breast cancer risks were observed. The authors, however, advise caution in interpreting these findings due to methodological limitations.

Evidence Statements (2004)

Risk of breast cancer increases with alcohol consumption. (III)

The Collaborative Group reported an increase of 7.1% in relative risk for each additional 10g per day intake of alcohol. (III)

There is no good evidence that the relative risk associated with increasing alcohol consumption is different for women with a family history compared to women as a whole. (III)

Recommendation

- Women with a family history should be informed that alcohol may increase their risk of breast cancer slightly. However, this should be considered in conjunction with any potential benefit of moderate alcohol intake on other conditions (such as heart disease) and adverse effects associated with excessive alcohol intake. **[2004]**

8.1.8 Smoking

Cigarette smoking may be associated with a small increase in breast cancer risk. The mechanism for this associated risk is unclear but it now appears that the earlier you start to smoke and the longer you smoke the greater the potential risk.

Clinical Evidence (2004) (see also full evidence review)

Results from a systematic review and a meta-analysis which assessed the association between smoking and breast cancer risk reached different conclusions, with the systematic review (Palmer, *et al.,*) finding either no, or very small positive, associations and the meta-analysis (Khuder, *et al.,*) finding significant increases in risk in ever, former and current smokers, with particularly high risks observed for premenopausal women and those who initiated smoking at an earlier age. The Collaborative group concluded that smoking has little or no independent effect on breast cancer risk.

Two North American observational studies both found that smoking significantly increased breast cancer risk. In the cohort study (Terry, *et al.,*), ever smoking (although not former smoking) increased risk; also smoking of very long duration and high intensity was associated with particularly high risk, with, for example, an 83% increase in breast cancer risk in women who smoked 20 or more cigarettes per day over 40 years or more, relative to never-smokers. In the case-control study (Band, *et al.,*), results suggested increases in risk in premenopausal women who smoked before a 1st pregnancy (but only when smoking was initiated within 5 years of onset of menarche) and in nulliparous premenopausal women. Postmenopausal women, however, were not at increased breast cancer risk, with some subsets of women showing a reduction in risk associated with smoking.

A third North American observational study found a significant 2.4-fold increase in breast cancer risk of smoking in sisters and daughters from families at high risk of breast and/or ovarian cancer.

Evidence Statements (2004)

There is no good evidence for an association between smoking and breast cancer. (IV)

In the Collaborative reanalysis, for women who reported they did not drink, compared to women who never smoked the relative risk of breast cancer was close to 1 in current or past smokers. (III)

A recent large meta analysis concluded that cigarette smoking increases breast cancer risk, with a higher risk in premenopausal women and in those who started smoking at an earlier age. (III)

Recommendation

- Women should be advised not to smoke, in line with current health advice. **[2004]**

8.1.9 Weight and physical activity

In scientific studies, obesity has been consistently associated with an increased risk of breast cancer among postmenopausal women. As is the case with reproductive risk factors, this relationship may be mediated by oestrogen production. Fat cells produce some oestrogen and obese postmenopausal women. It is less clear whether obesity is a risk factor for breast cancer in premenopausal women.

The effect of physical activity on breast cancer risk may be due at least in part to effects of exercise on the female hormones. Although the effects of obesity and physical inactivity on breast cancer risk are not as strong as the effects of previous breast disease or family history of breast cancer, they are important risk factors because they are modifiable.

Clinical Evidence (2004) (see also full evidence review)

An IARC report (2002b) reported findings from many cohort and case –control studies, which looked at reproductive and lifestyle factors. These were for general populations rather than those with a family history. A systematic review by Harvie, *et al.,* (2003) looked at the effect of central obesity on breast cancer risk.

Weight

Premenopausal women

A recent IARC report reported that for premenopausal women, in populations with a high incidence of breast cancer, those with high BMIs (over 28kg/m²) were found to have a slightly reduced breast cancer risk. It also reported that despite this reduced breast cancer incidence risk, the breast cancer mortality rate is not lower among heavier premenopausal women (IARC, 2002b: 237).

Harvie, *et al.,* (2003) found that waist measurement or waist to hip ration had little, if any effect, on risk of breast cancer. However they did find that using adjusted data (adjusted for BMI) showed a relative reduction (42%) in women with the smallest waist to hip ratio and that there was a relationship between central obesity and increased risk.

Postmenopausal women

A recent IARC report reported that more than 100 studies over nearly 30 years in populations in many countries have established that increased body weight increases breast cancer risk among postmenopausal women. It went on to say that almost all of these studies have shown that this association is largely independent of a wide variety of reproductive and lifestyle risk factors, also that recent studies have indicated that it is independent of the effect of physical activity. The association between being overweight and breast cancer appears to increase in a stepwise fashion with advancing age after the menopause (IARC, 2002b: 237). Harvie, *et al.,* (2003) found that women with the smallest waists (quintile) had a lower relative risk of breast cancer than those in the highest waist measurement quintile (39%, using unadjusted but pooled data) and similar findings for waist to hip measurement (34%, using unadjusted but pooled data). This relationship was attenuated when adjustment for BMI was made.

Physical activity

Most of the more than 30 epidemiological studies, conducted in Asia, Europe and North America, demonstrated lower breast cancer risk among the most physically active women. In 8 of the 14 cohort studies and in 14 of the 19 case-control studies, lower breast cancer risk was seen among women who were most active. The decrease in risk of breast cancer was, on average, about 20-40%. (IARC, 2002b: 238)

Evidence Statements (2004)

No specific evidence was found between the relationship between diet and exercise and familial breast cancer risk.

Moderate physical exercise is associated with a decrease risk in breast cancer in the general population. (III)

A high BMI is associated with a significant increase in post menopausal breast cancer risk in the general population. (III)

Recommendations

- Women should be advised on the probable increased postmenopausal risk of breast cancer from being overweight. **[2004]**
- Women should be advised about the potential benefits of physical exercise on breast cancer risk. **[2004]**

8.2 Chemoprevention for women with no personal history of breast cancer

Women at increased risk of breast cancer due to their family history have a limited range of strategies available to reduce their risk. For those for whom risk-reducing surgery is unsuitable or unacceptable, chemoprevention using drugs such as tamoxifen and raloxifene may represent a more acceptable means of risk reduction.

Tamoxifen and raloxifene (developed primarily for use as adjuvant treatments for hormone receptor positive breast cancer) reduce the risk of breast cancer for women without a personal history but who have an increased risk of the disease. Both drugs are approved by the US Food and Drug Administration for reducing breast cancer risk but not the European Medical Agency. However, even in the USA use of both drugs for breast cancer prevention is uncommon. This may be due to concerns over side effects of treatment and uncertainties around who should be offered chemoprevention.

All drugs have side effects and risks which are particularly important when they are being used to prevent other diseases. In the adjuvant setting, tamoxifen, is effective in pre and postmenopausal women, but can cause blood clots and cancer of the lining of the womb. In the adjuvant setting, raloxifene is only effective in postmenopausal women but can increase the risk of osteoporosis and bone fracture and can sometime cause intolerable muscle and joint aches and pains.

Although chemoprevention was investigated in the previous guidance, no recommendations were made on this topic. Since then, two trials which were reviewed in the previous guideline have been published and include updated results with longer follow-up times. It was therefore felt appropriate to re-investigate chemoprevention as part of this update.

Clinical Question: What is the effectiveness of chemoprevention for the reduction of the incidence of breast cancer in women with a family history of breast, ovarian or related (prostate/pancreatic) cancer?

Clinical Evidence (2013) (see also full evidence review)

Evidence Statements

Incidence of Breast Cancer

High quality evidence from two randomised trials (Fisher, *et al.,* 2005 and Cuzick, *et al.,* 2007; Table 8.1) suggests the incidence of breast cancer is lower in patients given tamoxifen than in those given a placebo (RR 0.65; 95% CI, 0.56-0.74).

Moderate quality evidence from one randomised trial (Vogel, *et al.,* 2006; Table 8.3) suggests tamoxifen and raloxifene have similar effectiveness when used as prophylaxis for breast cancer (RR 1.02; 95% CI, 0.82-1.28).

Very low quality evidence from a single randomised trial (Goss, *et al.,* 2011; Table 8.5) suggests the incidence of breast cancer is lower in patients given tamoxifen compared with those given a placebo (HR 0.35; 95% CI, 0.18-0.70).

Incidence of Endometrial Cancer

There is high quality evidence from a systematic review (Nelson, *et al.,* 2009; Table 8.1) that the incidence of endometrial cancer is higher in patients treated with prophylactic tamoxifen than in those given placebo (RR 2.13; 95% CI, 1.36-3.32).

There is moderate quality evidence (Nelson, *et al.,* 2009; Table 8.2) of uncertainty about the relative incidence of endometrial cancer in those given prophylactic raloxifene compared to those given placebo (RR 1.14; 95% CI, 0.65-1.98). This uncertainty is due to the low number of incident cases of endometrial cancer in the review.

There is moderate quality evidence from one randomised trial (Vogel, *et al.,* 2006; Table 8.3) of uncertainty about the relative incidence of endometrial cancer in patients who received tamoxifen compared to those given raloxifene (RR 0.62; 95% CI, 0.35-1.08). This uncertainty is due to the low number of incident cases of endometrial cancer in this trial.

High quality evidence, from one systematic review (Amir, *et al.,* 2011; Table 8.4), suggests the incidence of endometrial cancer is significantly lower in patients treated with an aromatase inhibitor than in those given tamoxifen (OR 0.22, 95% CI, 0.11-0.46).

Thromboembolic Events

There is high quality evidence (Nelson, *et al.,* 2009; Table 8.1 & 8.2) that thromboembolic events are more common in patients treated with tamoxifen or raloxifene when compared with placebo. For tamoxifen versus placebo RR = 1.93 (95% CI, 1.41-2.64) and for raloxifene versus placebo RR = 1.60 (95% CI, 1.15-2.23) .

High quality evidence (Vogel. *et al.,* 2006; Table 8.3) suggests that thromboembolic events are more common in patients treated with tamoxifen than in those given raloxifene (RR 0.70; 95% CI, 0.54-0.91).

There is high quality evidence (Amir, *et al.,* 2011; Table 8.4) that thromboembolic events are less common during prophylaxis with an aromatase inhibitor than with tamoxifen (OR 0.57; 95% CI, 0.46-0.64).

Fractures

High quality evidence suggests that fractures are less likely with prophylactic tamoxifen than with placebo (Fisher. *et al.,* 2006; Table 8.1; RR 0.68; 95% CI, 0.51-0.92) or with an aromatase inhibitor (Amir, *et al.,* 2011; Table 8.4; OR 0.68; 95% CI, 0.60-0.76). High quality evidence from a trial of tamoxifen versus raloxifene (Vogel, *et al.,* 2006; Table 8.3) suggests no difference in the relative fracture rates of the two treatments (RR 0.92; 95% CI, 0.69-1.22).

Table 8.1: GRADE Profile: What is the effectiveness of Tamoxifen versus Placebo for the reduction of the incidence of breast cancer in people with a family history of breast, ovarian or related (prostate/pancreatic) cancer?

Quality assessment						Summary of findings			
						No of patients		Effect	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Tamoxifen	Placebo	Relative (95% CI)	Quality
All Breast Cancer: Cuzick, *et al.,* (2007); Fisher, *et al.,* (2005) (follow-up 5-7 years)									
2	randomised trials	serious[1]	no serious inconsistency[2,3]	no serious indirectness	no serious imprecision[4]	347/10260 (3.4%)	538/10282 (5.2%)	Rate Ratio 0.65 (0.56 to 0.74)[5]	HIGH
Endometrial Cancer: Nelson, *et al.,* (2009) (follow-up median 4 years)									
3	randomised trials	no serious limitations	no serious inconsistency[3]	no serious indirectness	no serious imprecision	79/7682 (1%)	31/7719 (0.4%)	Rate Ratio 2.13 (1.36 to 3.32)	HIGH
Thromboembolic Events: Nelson, *et al.,* (2009) (follow-up median 4 years)									
4	randomised trials	no serious limitations	no serious inconsistency[3]	no serious indirectness	no serious imprecision	123/14198 (0.9%)	63/14223 (0.4%)	Rate Ratio 1.93 (1.41 to 2.64)	HIGH
Stroke: Nelson, *et al.,* (2009) (follow-up median 4 years)									
4	randomised trials	no serious limitations	no serious inconsistency[3]	no serious indirectness	no serious imprecision	59/14198 (0.4%)	43/14223 (0.3%)	Rate Ratio 1.36 (0.89 to 2.08)	HIGH
All Fractures: Fisher, *et al.,* (2006) (follow-up mean 74 months)									
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	80/6597 (1.2%)	116/6610 (1.8%)	Rate Ratio 0.68 (0.51 to 0.92)	HIGH
Ovarian Cancer: (Vicus, *et al.*,, 2009)									
1	observational studies	serious[6]	no serious inconsistency	no serious indirectness	not enough information in the paper to complete this section				VERY LOW

[1] Both included studies were large randomised trials, employing adequate methodology to randomise patients and subsequently analyse data. Both of the included studies are updated results of trials which have been previously reviewed and included in the original guideline. One study however was unblinded after the initial trial results were published.
[2] The two included randomised trials compared tamoxifen with placebo
[3] Trials varied in relation to follow-up times, women enrolled in the trials and in method of assessment of outcomes of interest, and these factors would be expected to affect the outcome of the trials, however overall, no inconsistency was observed in the individual trial results and therefore the studies were not downgraded.
[4] Large numbers randomised together with an extended period of follow-up mean that it is unlikely that the results are imprecise.
[5] RR refers to Rate Ratio (number of observed events divided by the total number of observed event-specific person-years at risk)
[6] Not a randomised trial and small numbers in the study

Table 8.2: GRADE Profile: What is the effectiveness of Raloxifene versus Placebo for the reduction of the incidence of breast cancer in people with a family history of breast, ovarian or related (prostate/pancreatic) cancer?

Quality assessment							Summary of findings			
							No of patients		Effect	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Raloxifene	Placebo	Relative (95% CI)	Quality
Thromboembolic Events: Nelson, *et al.,* (2009) (follow-up 4-5.5 years)										
2	randomised trials	no serious limitations	no serious inconsistency[1]	no serious indirectness	no serious imprecision	none	162/10173 (1.6%)	85/7633 (1.1%)	Rate Ratio 1.60 (1.15 to 2.23)	HIGH
Endometrial Cancer: Nelson, *et al.,* (2009) (follow-up 4-5.5 years)										
2	randomised trials	no serious limitations	no serious inconsistency[1]	no serious indirectness	Serious[2]	none	30/7860 (0.4%)	22/4081 (0.5%)	Rate Ratio 1.14 (0.65 to 1.98)	MODERATE
Cataracts/Cataract surgery: Nelson, *et al.,* (2006) (follow-up 4-5.5 years)										
2	randomised trials	no serious limitations	no serious inconsistency[1]	no serious indirectness	no serious imprecision	none	665/10117 (6.6%)	551/7600 (7.3%)	Rate Ratio 0.93 (0.84 to 1.04)	HIGH
Coronory Heart Disease Events: Nelson *et al.,* (2009) (follow-up 4-5.5 years)										
2	randomised trials	no serious limitations	no serious inconsistency[1]	no serious indirectness	no serious imprecision	none	297/8554 (3.5%)	256/6760 (3.8%)	Rate Ratio 0.96 (0.67 to 1.38)	HIGH

[1] Trials varied in relation to follow-up times, women enrolled in the trials and in method of assessment of outcomes of interest, and these factors would be expected to affect the outcome of the trials, however overall, no inconsistency was observed in the individual trial results and therefore the studies were not downgraded.
[2]There were very few events recorded and the confidence interval crosses 0 therefore the results are considered to be imprecise as it is unclear whether there is treatment effect or not.

Table 8.3: GRADE Profile: What is the effectiveness of Tamoxifen versus Raloxifene for the reduction of the incidence of breast cancer in people with a family history of breast, ovarian or related (prostate/pancreatic) cancer?

Quality assessment						Summary of findings			
						No of patients		Effect	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Tamoxifen	Raloxifene	Relative (95% CI)	Quality
Breast Cancer (Invasive): Vogel, *et al.,* (2006) (follow-up median 47 months)									
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	Serious[2]	163/9726 (1.7%)	168/9745 (1.7%)	Rate Ratio 1.02 (0.82 to 1.28)[4]	MODERATE
Breast Cancer (non-invasive): Vogel, *et al.,* (2006) (follow-up median 47 months)									
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	Serious[2]	57/9726 (0.6%)	80/9745 (0.8%)	Rate Ratio 1.40 (0.98 to 2)[4]	MODERATE
Uterine Cancer: Vogel, *et al.,* (2006) (follow-up median 47 months)									
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	Serious[2]	36/9726 (0.4%)	23/9745 (0.2%)	Rate Ratio 0.62 (0.35 to 1.08)[4]	MODERATE
Thromboembolic Events: Vogel, *et al.,* (2006) (follow-up median 47 months)									
1	randomised trials[5]	no serious limitations[1]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	141/9726 (1.4%)	100/9745 (1%)	Rate Ratio 0.70 (0.54 to 0.91)	HIGH
All Fractures: Vogel, *et al.,* (2006) (follow-up median 47 months[5])									
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	0/0 (0%)	0/0 (0%)	Not estimable	HIGH
Cataracts: Vogel, *et al.,* (2006) (follow-up median 47 months)									
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	394/8334 (4.7%)	313/8329 (3.8%)	Rate Ratio 0.79 (0.68 to 0.92)	HIGH
Ischaemic Heart Disease: Vogel, *et al.,* (2006) (follow-up median 47 months[5])									
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	114/9726 (1.2%)	126/9745 (1.3%)	Rate Ratio 0 (0 to 0)	HIGH
Health Related Quality of Life: Land, *et al.,* (2006)									
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	Serious[6]	No data			MODERATE

[1] Large, multicentre, double blind randomised trial. Randomisation method used was the biased coin minimisation method with stratification of age, race/ethnicity, history of LCIS and 5 year predicted risk of breast cancer.
[2]Due to the small number of events reported, the confidence intervals cross the line of no effect and therefore there is a degree of uncertainty over the true effect.
[3] Large numbers in the trial together with an extended period of follow-up mean that it is unlikely that the results are imprecise (N=19747 patients randomised and 19471 patients analysed) despite the low number of events observed.
[4] RR relates to Risk Ratio (number of observed events divided by the total number of observed event-specific person-years at risk)
[5] Minimum follow-up=64 months; Maximum follow-up=77 months
[6]Although the study was designed as a randomised trial, the entire trial population did not complete in the quality of life assessments and the numbers completing the questionnaires declined at each assessment from baseline

Table 8.4: GRADE Profile: What is the effectiveness of Aromatase Inhibitor versus Tamoxifen for the reduction of breast cancer incidence in people with a family history of breast, ovarian or related (prostate/pancreatic) cancer?

Quality assessment						Summary of findings			
						No of patients		Effect	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Aromatase Inhibitor	Tamoxifen	Relative (95% CI)	Quality
Endometrial Cancer: Amir, *et al.,* (2011) (follow-up 51-100 months)									
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness[1]	no serious imprecision	0/0 (0%)[2]	0/0 (0%)[2]	Not estimable[3]	HIGH
Venous Thrombosis: Amir, *et al.,* (2011) (follow-up 51-100 months)									
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness[1]	no serious imprecision	0/0 (0%)[2]	0/0 (0%)[2]	Not estimable[4]	HIGH
Cardiovascular Disease: Amir, *et al.,* (2011) (follow-up 51-100 months)									
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	0/0 (0%)[2]	0/0 (0%)[2]	Not estimable[5]	HIGH
Bone Fractures: Amir, *et al.,* (2011) (follow-up 51-100 months)									
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness[1]	no serious imprecision	0/0 (0%)[2]	0/0 (0%)[2]	Not estimable[3]	HIGH
Other Secondary Cancers: Amir, *et al.,* (2011) (follow-up 51-100 months)									
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness[1]	no serious imprecision	0/0 (0%)[2]	0/0 (0%)[2]	Not estimable[6]	HIGH

[1] Although the population for these trials included women with breast cancer and not just unaffected women with family history, there was an a priori decision to include such trials on the basis that the adverse effects of treatment will not differ in the different populations. Therefore this will not be downgraded for indirectness.
[2] Numbers not reported and the rates reported in the systematic review are for all comparisons combined, not just AI versus Tamoxifen so these cannot be used to work out the number of events.
[3] p<0.001
[4] OR is for two trials comparing AI (anastrozole and letrozole) with Tamoxifen only.
[5] p=0.01
[6] p=0.83

Table 8.5: GRADE Profile: What is the effectiveness of Aromatase Inhibitor (Exemestane) versus Placebo for the reduction of breast cancer incidence of breast cancer in people with a family history of breast, ovarian or related (prostate/pancreatic) cancer?

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Aromatase Inhibitor	Placebo	Relative (95% CI)	
Invasive Breast Cancer Incidence (Goss, *et al.*,, 2011) (follow-up median 35 months; Mammography[1])										
1	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	11/2285 (0.5%)[5]	32/2275 (1.4%)[6]	HR 0.35 (0.18 to 0.70)[7]	VERY LOW

[1] Annual mammography was performed equally in both groups
[2] Short follow-up time (median 3 years)
[3] *BRCA* carriers were specifically excluded from the study and patients with a previous history of breast cancer were included.
[4] The number of events recorded during the study was small (n=66)
[5] Annual incidence rate for invasive breast cancer was reported as being 0.19%
[6] Annual incidence rate for invasive breast cancer was reported as being 0.55%
[7] Favouring Exemestane over placebo

Cost effectiveness evidence (2013)

A literature review of published cost-effectiveness analysis did not identify any relevant papers. No further health economic analysis was undertaken as other topics were agreed as a higher priority for investigation.

Recommendations

- Healthcare professionals within a specialist genetics clinic should discuss and give written information on the absolute risks and benefits (including side effects of drugs and the extent of risk reduction) of all options for preventive treatment to women at high risk of breast cancer. **[new 2013]**
- Offer tamoxifen[32] for 5 years to pre-menopausal women at high risk of breast cancer unless they have a past history of thromboembolic disease or endometrial cancer. **[new 2013]**
- Offer tamoxifen[32] or raloxifene[33] for 5 years to post-menopausal women at high risk of breast cancer unless they have a past history of thromboembolic disease or endometrial cancer. **[new 2013]**
- Do not offer tamoxifen[32] or raloxifene[33] to women who were at high risk of breast cancer but have had a bilateral mastectomy. **[new 2013]**
- Healthcare professionals within secondary care and/or specialist genetics clinic should discuss and give written information on the absolute risk and benefits (including side effects of drugs and the extent of risk reduction) of all options for preventive treatment to women at moderate risk of breast cancer. **[new 2013]**
- Consider prescribing tamoxifen[32] for 5 years to pre-menopausal women at moderate risk of developing breast cancer within the next 10 years. **[new 2013]**
- Consider prescribing tamoxifen[32] or raloxifene[33] for 5 years to post-menopausal women at moderate risk of developing breast cancer within the next 10 years. **[new 2013]**
- Do not continue treatment with tamoxifen[32] or raloxifene[33] beyond 5 years. **[new 2013]**
- Inform women that they must stop tamoxifen[32] at least:
  - 3 months before trying to conceive
  - 6 weeks before surgery **[new 2013]**

Linking evidence to recommendations

The aim of this topic was to determine the effectiveness of chemoprevention for the reduction of the incidence of breast cancer in women with a family history of breast, ovarian or a related (prostate/pancreatic) cancer.

[32] At the time of consultation (January 2013), tamoxifen did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[33] At the time of consultation (January 2013), raloxifene did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

The GDG considered the outcomes of development of cancer, adverse events, health related quality of life and overall survival to be the most important to this question. All outcomes were reported in the evidence except overall survival.

During the initial literature searches for this topic the GDG agreed to widen the population to include all patients diagnosed with breast cancer to help inform the outcome of adverse events as it was agreed that the adverse events of treatment would not differ for patients with or without a family history.

The quality of the evidence, as assessed by GRADE, was high for all outcomes in studies comparing tamoxifen with placebo except for incidence of ovarian cancer where the quality of evidence was assessed as very low. For studies comparing raloxifene with placebo, the quality of evidence was again high for all outcomes except endometrial cancer occurrence which was assessed as moderate quality. For studies comparing tamoxifen and raloxifene, the evidence for the incidence of breast cancer (invasive and non-invasive) and uterine cancer was assessed as moderate quality. For adverse events the available evidence was of high quality. The quality of the evidence was high for all outcomes in studies comparing any aromatase inhibitors with tamoxifen. For the comparison of exemestane with tamoxifen the quality of the evidence was assessed as very low for the one reported outcome of incidence of invasive breast cancer.

Although aromatase inhibitors were included as an intervention for this topic, and several trials reported on their effectiveness, the GDG were not able to recommend the use of a particular drug. This was because the relevant trials within the systematic review did not differentiate between the different aromatase inhibitors, choosing instead to have a single arm consisting of all aromatase inhibitors combined compared to tamoxifen alone. In addition, although there was a trial which compared exemestane with tamoxifen, it only reported one outcome and was of very low quality. The GDG therefore did not consider this sufficient to make a recommendation on the use of exemestane.

The GDG noted that there was high quality evidence that shows tamoxifen is effective in reducing breast cancer incidence when used for chemoprevention in pre and post menopausal women who do not have a diagnosis of breast cancer. There was also high quality evidence which suggests tamoxifen and raloxifene have similar effectiveness when used for chemoprevention in post menopausal women who do not have a diagnosis of breast cancer.

Although neither agent has a UK marketing authorisation for chemoprevention in women who do not have a diagnosis of breast cancer, the GDG felt that the evidence of benefit was sufficiently strong to outweigh the potential harms of side effects and recommended their use for women at high risk of breast cancer. For women at moderate risk of breast cancer, the GDG were less certain of the balance between benefits and harms. However they agreed that it would not be appropriate to prevent women at moderate risk of breast cancer from accessing these drugs, providing they were aware of the risks and benefits. The GDG therefore agreed that tamoxifen and raloxifene could be considered for use in women with moderate risk breast cancer.

The GDG agreed, based on the evidence, that recommending the use of either tamoxifen or raloxifene could increase the frequency of side effects of treatment and women would need to be reminded of their risk should they opt for chemoprevention. The GDG noted that providing appropriate written and verbal information on risks and benefits would allow women the opportunity to make an informed choice. Women would also have the opportunity to discuss their treatment choices and their absolute risk and benefits with healthcare professionals in secondary and/or the specialist genetics service in order to benefit from

more appropriate and tailored management advice. The GDG agreed that this could also bring psychological benefit to patients.

The GDG also thought it useful to include a recommendation to remind clinicians not to offer chemoprevention for women originally at high risk of breast cancer who have had bilateral mastectomies. The GDG also noted that fertility in pre-menopausal women could be affected as a result of taking these particular chemopreventive agents.

The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis was undertaken in this area. The GDG agreed that there could be potential cost savings by reducing the incidence of breast cancer in this population of patients. However the GDG also acknowledged that these recommendations could lead to an increase in drug costs and a significant change to current clinical practice. There would also be additional costs as a result of testing for hormone status in pre- and post-menopausal women.

Because existing evidence for this topic did not report a particular, named aromatase inhibitor as a chemopreventive agent, the GDG decided to recommend further research in this area. The proposal is to compare the clinical and cost effectiveness of different aromatase inhibitors with tamoxifen as chemopreventative agents to reduce the incidence of breast cancer in women with a family history of breast or ovarian cancer.

Research recommendation

- A randomised controlled trial is recommended to compare the clinical and cost effectiveness of aromatase inhibitors and tamoxifen for reducing the incidence of breast cancer in women with a family history of breast or ovarian cancer. **[new 2013]**

8.3 Risk-reducing surgery

Women at risk of developing breast or ovarian cancer due to their family history may consider surgery as an option to reduce this risk. This surgery may include either a risk-reducing bilateral mastectomy and/or a risk-reducing bilateral salpingo-oophorectomy. Surgery of this nature carries risks to the women including the immediate and late complications from surgery as well as long term psychosocial and sexual consequences. Also a bilateral salpingo-oophorectomy will lead to a surgically induced menopause. For these reasons the risks of surgery need to be balanced against the future risk of breast or ovarian cancer.

When discussing risk-reducing surgery it is recognised that there are some circumstances where this option may be inappropriate. These circumstances include those with comorbidites which may increase the risk of surgery and those with a poor prognosis from their breast cancer who may not benefit from surgery.

The previous guideline only included women who had no personal history of breast cancer. In this section consideration is given to women who have a family history of breast cancer including those with no personal history of breast cancer and those with a personal history of breast cancer.

8.3.1 Risk-reducing mastectomy for women with no personal history of breast cancer

Bilateral mastectomy may be used as a risk-reducing strategy in women at increased risk of breast cancer due to their family history. The aim of surgery is to remove the majority of the 'at risk' breast tissue with a corresponding reduction in breast cancer risk. This type of major surgery is one that will need considerable discussion and the women concerned may need time to consider this in detail to allow them to reach an informed decision that they are comfortable with.

There are documented cases of subsequent breast cancer development after both subcutaneous (nipple-areola sparing) and total mastectomy. Bilateral risk-reducing mastectomy is a major undertaking for any woman. Careful patient selection and pre-operative preparation is required. The decision to opt for surgery is most appropriately patient led rather than clinician led.

Clinical Evidence (2004) (see also full evidence review)

No evidence has been identified which compares the effectiveness of total versus subcutaneous risk-reducing mastectomy in terms of reducing the incidence of breast cancer. Case reports in the literature show that neither total nor subcutaneous risk-reducing mastectomy are 100% effective in preventing breast cancer (Goodnight, *et al.,* 1984; Eldar, *et al.,* 1984; Ziegler, *et al.,* 1991; Willemsen, *et al.,* 1998).

In a case series of women with a family history of breast cancer or a *BRCA1*/*BRCA2* mutation who underwent total risk-reducing mastectomy (including nipple/areolar complex), there was no evidence of disease after a median follow-up of 2.5 years (range 1-5.9 years) in 79 women with no previous history of breast cancer, ovarian cancer or ductal carcinoma in situ, (Contant, *et al.,* 2002).

The overall findings from 2 observational studies and 3 decision analysis studies suggest that risk-reducing subcutaneous/total mastectomy has a beneficial effect in terms of significantly reducing the risk of breast cancer in women with a family history of breast cancer, or with *BRCA1* and *BRCA2* mutations. One of the observational studies found that risk-reducing mastectomy was also associated with a reduction in breast cancer mortality in women with a family history of breast cancer.

Results from 7 studies which evaluated various psychosocial outcomes after risk-reducing mastectomy, two of which had lengthy follow-up periods, show that risk-reducing mastectomy is associated overall with fairly high levels of satisfaction and reduced anxiety and psychological morbidity amongst women who undergo this procedure. A number of the studies suggest that the provision of pre-surgical multidisciplinary support was likely to have had a bearing on these findings. A minority of women, however, do express regrets and experience adverse psychosocial events following their surgery.

There is no clear evidence on the optimal surgical technique for risk-reducing mastectomy.

Evidence Statements (2004)

Risk-reducing mastectomy reduces the risk of breast cancer. (III)

There are case reports of breast cancer in women who have had sub-cutaneous mastectomy (nipple/areola sparing), and total mastectomy. (IV)

Total mastectomy is likely to be more effective than sub-cutaneous mastectomy (nipple/areola sparing) in reducing the incidence of breast cancer. (IV)

Risk-reducing mastectomy will not prevent the development of all breast cancers. (III)

At risk-reducing mastectomy some women are found to have cancer. (IV)

Various observational studies report a risk reduction for breast cancer of about 90% in populations of those considered as moderate or high risk and *BRCA1* or *BRCA2* gene carriers. (III)

The majority of women undergoing risk-reducing mastectomy are happy with their decision. (IV)

For many women, cancer worry decreases after risk-reducing mastectomy. (IV)

A small proportion of women express regret about their decision for bilateral risk-reducing mastectomy and would not choose this option again. These women were more likely to have had the option of risk-reducing mastectomy raised by a clinician rather than by themselves. (IV)

The effectiveness of preoperative counselling has not been formally evaluated. (IV)

Recommendations

- Bilateral risk-reducing mastectomy is appropriate only for a small proportion of women who are from high-risk families and should be managed by a multidisciplinary team. **[2004]**
- Bilateral mastectomy should be raised as a risk-reducing strategy option with all women at high risk. **[2004]**
- Women considering bilateral risk-reducing mastectomy should have genetic counselling in a specialist cancer genetics clinic before a decision is made. **[2004]**
- Discussion of individual breast cancer risk and its potential reduction by surgery should take place and take into account individual risk factors, including the woman's current age (especially at extremes of age ranges). **[2004]**
- Family history should be verified where no mutation has been identified before bilateral risk-reducing mastectomy. **[2004]**
- Where no family history verification is possible, agreement by a multidisciplinary team should be sought before proceeding with bilateral risk-reducing mastectomy. **[2004]**
- Pre-operative counselling about psychosocial and sexual consequences of bilateral risk-reducing mastectomy should be undertaken. **[2004]**
- The possibility of breast cancer being diagnosed histologically following a risk-reducing mastectomy should be discussed pre-operatively. **[2004]**
- All women considering bilateral risk-reducing mastectomy should be able to discuss their breast reconstruction options (immediate and delayed) with a member of a surgical team with specialist oncoplastic or breast reconstructive skills. **[2004]**
- A surgical team with specialist oncoplastic/breast reconstructive skills should carry out risk-reducing mastectomy and/or reconstruction. **[2004]**
- Women considering bilateral risk-reducing mastectomy should be offered access to support groups and/or women who have undergone the procedure. **[2004]**

8.3.2 Risk-reducing oophorectomy for women with no personal history of breast cancer

Risk-reducing oophorectomy may be considered as a risk-reducing strategy for pre-menopausal women at an increased risk of developing breast cancer. *BRCA1* and *BRCA2* carriers also have an increased risk of fallopian tubes and peritoneal cancers.

Clinical Evidence (2004) (see also full evidence review)

The findings from 3 observational and 3 decision analysis studies suggest that risk-reducing oophorectomy has a beneficial effect in terms of significantly reducing the risk of breast and/or various gynaecological cancers in women with *BRCA1* and/or *BRCA2* mutations. Postoperative complications were reported in a minority of women in one of the observational studies, and in a review of hospital records in Canada, 14% of women who underwent risk-reducing oophorectomy experienced adverse effects from the surgery.

In terms of psychosocial outcomes the impact of risk-reducing oophorectomy reported in a small number of smallish studies gave inconsistent findings. Findings about issues such as cancer worry and general satisfaction with the procedure were varied in different studies. These tended to depend upon factors such as age, menopausal status and so on.

Evidence Statements (2004)

Risk-reducing oophorectomy before menopause is effective in reducing breast cancer risk. (III)

In the general female population, undergoing a risk-reducing oophorectomy at or below 40 years of age reduces the risk of breast cancer by between 50-75%. (III)

For women with a family history (including *BRCA1*, *BRCA2* carriers) the relative risk-reduction (50-75%) is similar but absolute risk reduction will be greater. (III)

The use of HRT following oophorectomy may have an impact (negative) on the level of risk-reduction, but there is no good evidence. (IV)

There is a lack of prospective studies of psychosexual outcomes in women with a family history of breast cancer.

Anxiety may be a significant motivating factor for surgery in women seeking risk-reducing oophorectomy. (IV)

The evidence with respect to the reduction of cancer worry and of increased general psychological distress following surgery is conflicting (from retrospective studies). (IV)

Negative impacts of surgery on sexual functioning and menopausal symptoms have been reported in small, qualitative, retrospective studies. (IV)

Unmet needs for information about expected menopausal symptoms and safety in using HRT have been reported. (IV)

Recommendations

- Risk-reducing bilateral oophorectomy is appropriate only for a small proportion of women who are from high risk families and should be managed by a multidisciplinary team. **[2004]**
- Information about bilateral oophorectomy as a potential risk-reducing strategy should be made available to women who are classified as high risk. **[2004]**
- Family history should be verified where no mutation has been identified before bilateral risk-reducing oophorectomy. **[2004]**
- Where no family history verification is possible, agreement by a multidisciplinary team should be sought before proceeding with bilateral risk-reducing oophorectomy. **[2004]**
- Any discussion of bilateral oophorectomy as a risk-reducing strategy should take fully into account factors such as anxiety levels on the part of the woman concerned. **[2004]**
- Healthcare professionals should be aware that women being offered risk-reducing bilateral oophorectomy may not have been aware of their risks of ovarian cancer as well as breast cancer and should be able to discuss this. **[2004]**
- The effects of early menopause should be discussed with any woman considering risk-reducing bilateral oophorectomy. **[2004]**
- Options for management of early menopause should be discussed with any woman considering risk-reducing bilateral oophorectomy, including the advantages, disadvantages and risk impact of HRT. **[2004]**
- Women considering risk-reducing bilateral oophorectomy should have access to support groups and/or women who have undergone the procedure. **[2004]**
- Women considering risk-reducing bilateral oophorectomy should be informed of possible psychosocial and sexual consequences of the procedure and have the opportunity to discuss these issues. **[2004]**
- Women not at high risk who raise the possibility of risk-reducing bilateral oophorectomy should be offered appropriate information, and if seriously considering this option should be offered referral to the team that deals with women at high risk. **[2004]**
- Women undergoing bilateral risk-reducing oophorectomy should have their fallopian tubes removed as well. **[2004]**

8.3.3 HRT for women with no personal history of breast cancer who have had a bilateral salpingo-oophorectomy before the natural menopause.

Women found to be at risk for breast or ovarian cancer because of an inherited *BRCA1* and *BRCA2* mutation may undergo a bilateral salpingo-oophorectomy (BSO) to reduce their chances of developing ovarian (and breast) cancer. Where this is done before the natural menopause, a surgical menopause will be precipitated and women may consider hormone replacement for symptom relief and/ or prevention of accelerated osteoporosis or heart disease. There has been much publicity regarding the increased risks of breast cancer associated with HRT but most of these data come from studies where replacement is taken after the natural menopause. This question addresses the risks and benefits in the specific group of high risk women but before the natural menopause. Different types of HRT will be considered since women who have intact uteri will need progesterone in their replacement (combined HRT), whilst those with a hysterectomy can take oestrogen preparations only.

Clinical Question: What are the risks and benefits of HRT for women under the age of 50, with a *BRCA1* or *BRCA2* mutation who have undergone a bilateral salpingo-oophorectomy?

Clinical Evidence (new 2013) (see also full evidence review)

Evidence Statements

Risk of Breast Cancer

Three observational studies (Eisen, *et al.,* 2008; Rebbeck, *et al.,* 2005 and Gabriel, *et al.,* 2009: table 8.6) of very low quality reported on the risk of breast cancer associated with HRT in this population. Their results however, are conflicting possibly due to variations in study methodology, populations and outcome assessment.

Eisen *et al.,* (2008) reported that women who had used hormone therapy had a lower breast cancer risk than women who had never used hormone therapy (OR=0.58; 95% CI=0.35-0.96, p=0.03). Rebbeck, *et al.,* (2005) reported 8% of bilateral prophylactic oophorectomy (BPO) patients and 21% of non-BPO patients were diagnosed with a first primary breast cancer during follow-up (HR=0.40, 95% CI, 0.18-0.91) irrespective of HRT use.

Gabriel, *et al.,* (2009) reported that in 17 women using oestrogen only HRT, 3 subsequently developed breast cancer while none of the women taking combined or 'unknown' HRT preparations developed breast cancer. Among the 17 women who developed breast cancer, 9 had a BRCA1 mutation and 8 had a BRCA2 mutation.

Bone Protection

There is uncertainty about whether HRT provides bone protection in this population. One non comparative observational study (Challberg, *et al.,* 2011; table 8.9) reported on the role of HRT in bone protection: 38% of women scanned had abnormal results. 28% reported bone mass consistent with osteopenia and 10% indicated osteoporosis.

Endocrine Symptoms

There is uncertainty about whether HRT affects endocrine in this population. Two observational studies (Challberg, *et al.,* 2011 and Madalinska, *et al.,* 2006) of very low quality (Table 8.7) reported endocrine symptoms as an outcome, both studies appear to use different methods for assessing symptoms in the study population and it is therefore not possible to make a definitive statement as to the effectiveness of HRT for endocrine symptoms.

Sexual Functioning

Very low quality evidence (Madalinksa, *et al.,* 2006; Table 8.8) suggests no significant difference in sexual activity between women who are *BRCA1/2* mutation carriers and have prophylactic bilateral salpingo-oophorectomy (PBSO) and with those opting for gynaecological screening. This study did not report the relative or absolute rates of sexual activity so the relevance of its findings is unclear.

Overall survival, incidence of primary peritoneal cancer, cardiovascular disease or health related quality

There was no evidence about overall survival, incidence of primary peritoneal cancer, cardiovascular disease or health related quality of life related to HRT in this population.

Table 8.6: GRADE Profile: What is the effectiveness of HRT for women who have had a bilateral salpingo-oophorectomy before the natural menopause for reducing the risk of breast cancer?

Quality assessment							Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	
Risk of Breast Cancer							
Eisen A *et al.,* (2008); Gabriel C *et al.,* (2009); Rebbeck T *et al.,* (2005)							
3	observational studies	very serious[1]	serious[2]	serious[4]	serious[3]	none	VERY LOW

[1] All studies were retrospective analysis of existing cohorts and the numbers involved in the individual studies were sufficiently small so to render the studies underpowered for the detection of any significant differences.
[2] Due to the small numbers, differing methods of assessing and reporting outcomes and a lack of studies reporting the same outcomes, it is not possible to comment with any confidence on the degree of consistency across the included studies.
[3] The numbers in the individual studies are too low to give precise results.
[4] The population included in Eisen *et al.,* (2008) included primarily women who had undergone natural menopause rather than surgical.

Table 8.7: GRADE Profile: What is the effectiveness of HRT for women who have had a bilateral salpingo-oophorectomy before the natural menopause for reducing endocrine symptoms?

Quality assessment							
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
Endocrine Symptoms							
Challberg, *et al.,* (2011); Madalinska, *et al.,* (2006)							
2	observational studies	very serious[1]	serious[2]	no serious indirectness	serious[3]	none	VERY LOW

[1] All studies were retrospective analysis of existing cohorts and the numbers involved in the individual studies were sufficiently small so to render the studies underpowered for the detection of any significant differences.
[2] Due to the small numbers, differing methods of assessing and reporting outcomes and a lack of studies reporting the same outcomes, it is not possible to comment with any confidence on the degree of consistency across the included studies.
[3] The numbers in the individual studies are too low to give precise results.

Table 8.8: GRADE Profile: What is the effectiveness of HRT for women who have had a bilateral salpingo-oophorectomy before the natural menopause on sexual functioning?

Quality assessment							
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
Sexual Functioning (Better indicated by lower values)							
Madalinska, *et al.,* (2006)							
1	observational studies	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	VERY LOW

[1] Retrospective case series
[2]Results included patients undergoing oophorectomy and patients choosing gynaecological screening.
[3]The numbers in the individual study are too low to give precise results despite the fact that more than 1000 patients were eligible, the results from this study include fewer than 500 patients total and only 164 patients had undergone prophylactic oophorectomy.

Table 8.9: GRADE Profile: What is the effectiveness HRT for women who have had a bilateral salpingo-oophorectomy before the natural menopause for bone protection?

Quality assessment							
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Bone Protection (Better indicated by lower values)							
Challberg, *et al.,* (2011)							
1	observational studies	serious[1]	no serious inconsistency	serious[2]	erious[3]	none	VERY LOW

[1]Retrospective Case Series
[2]The study does not specifically assess osteoporosis which was the outcome identified as being the important outcome for the topic, though it does report on indications of osteoporosis.
[3]Due to the small numbers being assessed

Cost effectiveness evidence (2013)

A literature review of published cost-effectiveness analysis did not identify any relevant papers. No further health economic analysis was undertaken as it was agreed that cost effectiveness analysis was unlikely to contribute additional relevant information to the decision on whether or not to use hormone replacement therapy, which is governed by safety issues. In addition the value of modelling was considered limited due to the small number of people involved.

Recommendations

- When women with no personal history of breast cancer have either a *BRCA1* or *BRCA2* mutation or a family history of breast cancer and they have had a bilateral salpingo-oophorectomy before their natural menopause, offer them:
  - combined HRT if they have a uterus
  - oestrogen only HRT if they don't have a uterus

  up until the time they would have expected natural menopause. **[new 2013]**
- Manage menopausal symptoms occurring when HRT is stopped in the same way as symptoms of natural menopause. **[new 2013]**

Linking evidence to recommendations

The aim of this topic was to identify the risks and benefits of hormone replacement therapy for women under the age of 50, with BRCA1 or BRCA2 mutation who have undergone a bilateral-salpingo-oophorectomy.

The GDG considered the outcomes of incidence of cardiovascular disease, incidence of osteoporosis, health related quality of life, overall survival, risk of breast cancer and risk of primary peritoneal cancer to be the post most important to the question. No evidence was reported for overall survival, incidence of cardiovascular disease, incidence of primary peritoneal cancer or health-related quality of life. The GDG agreed to consider the additional outcomes of sexual functioning, endocrine symptoms and bone mineral density changes as they considered these to be indirectly related to the outcome of health related quality of life and osteoporosis. The quality of the evidence was very low for all reported outcomes on GRADE assessment.

The GDG recognised that there are concerns regarding the increased risk of breast cancer associated with hormone replacement therapy. However, the GDG noted that there was no clear evidence that taking HRT increases the risk of breast cancer in women under 50 who have had their ovaries removed. The GDG also noted that HRT can reduce the chances of a women developing osteoporosis, as well as reducing the number of endocrine symptoms such as hot flushes, mood alteration and sexual dysfunction which are associated with the menopause. Therefore, it was the opinion of the GDG that the benefits of taking HRT outweighed any associated risk.

The GDG noted that no relevant published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The opinion of the GDG, based on their clinical experience, was that there may be potential additional costs associated with increased prescribing of HRT in those women who have undergone a bilateral-salpingo-oophorectomy. However, the GDG noted that there may be cost savings made from a reduction in treatment costs for the side-effects of the menopause, especially osteoporosis.

Therefore, the GDG recommend that women with no personal history of breast cancer with either a *BRCA1* or *BRCA2* mutation, or a family history of breast cancer who have undergone a bilateral-salpingo-oophorectomy before the natural menopause are offered, hormone replacement therapy up until the time they would have expected the natural menopause. The GDG also recommended that menopausal symptoms occurring when hormone replacement therapy is stopped are managed in the same way as symptoms occurring from the natural menopause.

8.3.4 Risk-reducing breast or ovarian surgery for people with a personal history of breast cancer.

The decision to consider risk-reducing surgery is complex and includes weighing up the risk of dying from the existing or treated cancer as well as the risk of developing a new primary breast or ovarian cancer.

The prognosis of any breast cancer depends on stage, tumour biology and treatment efficacy. Algorithms exist to predict the probability of distant relapse and death depending on these parameters. This assessment is an important part of the decision to consider risk-reducing surgery.

For patients with an inherited risk of breast and ovarian cancer, risk-reducing surgery is often considered though the uptake is variable. Bilateral risk-reducing mastectomy removes most of the breast tissue and consequently reduces the risk of developing breast cancer in the future. It is however not possible to remove all breast tissue and even with risk-reducing surgery there will be a small risk of future breast cancer. Removal of both ovaries and fallopian tubes reduces the future risk of developing both ovarian cancer and breast cancer. Despite surgery there will remain a small risk of developing primary peritoneal carcinoma.

Surgical procedures are however associated with risks. For mastectomy these risks include immediate complications of surgery and in the longer term the need for cosmetic revision procedures as well as the psychological implications of the surgery. Removal of the ovaries induces a surgical menopause which renders the women infertile as well as exposing the women to risks of premature oestrogen deficiency with loss of bone density, higher risks of cardiovascular disease and menopausal symptoms.

Clinical Question: What level of risk indicates that risk-reducing surgery is a viable option?

Clinical Evidence (new 2013) (see also full evidence review)

Evidence Statements

Risk-reducing Mastectomy

Overall Survival

Very low quality evidence suggests contralateral risk-reducing mastectomy improves overall survival (Lostumbo, *et al.,* 2010; Boughey, *et al.,* 2010; Table 8.10). In their systematic review of observational studies, Lostumbo, *et al.,* (2010) estimated 15 year overall survival with risk-reducing mastectomy as 64% versus 48% without (HR 0.6; 95% CI, 0.5-0.72).

Breast Cancer Incidence

Very low quality evidence consistently shows that contralateral risk-reducing mastectomy reduces the incidence of breast cancer (Lostumbo, *et al.,* 2010; Domchek, *et al.,* 2010; Evans, *et al.,* 2009 and Kaas, *et al.,* 2010; Table 8.10). In Lostumbo, *et al.,* (2010) the incidence of breast cancer was 0/64 in those treated with contralateral risk-reducing mastectomy versus 36/82 in those who were not. Evans *et al.,* (2009) observed no incident breast cancers during 1178.58 person years follow-up after risk-reducing mastectomy versus 13.15 expected.

Health Related Quality of Life

Very low quality evidence suggests most women are satisfied with their decision to undergo contralateral risk-reducing mastectomy. In their systematic review Lostumbo, *et al.,* (2010) found 83-94% of women were satisfied with their choice for risk-reducing mastectomy and no significant difference was observed in satisfaction with their cosmetic outcome when compared with women who did not have contralateral risk-reducing mastectomy (21.1% versus 15%).

Risk-reducing Bilateral Salpingo-Oophorectomy

Breast Cancer Incidence

Very low quality evidence (Rebbeck, *et al.,* 2009; Metcalfe, *et al.,* 2011; Table 8.11) shows risk-reducing bilateral salpingo-oophorectomy (RBSO) is associated with a lower incidence of breast cancer when compared with women who did not undergo RBSO. The relative reduction in breast cancer risk with RBSO versus no RBSO was 51%; HR 0.49; 95% CI, 0.37-0.65 (Rebbeck, *et al.,* 2009).

Gynaecological Cancers

Very low quality evidence (Rebbeck, *et al.,* 2009 Table 8.11) suggests the incidence of gynaecological cancers is lower in women who had RBSO compared with those who did not: Relative reduction in risk of 79%; HR, 0.21; 95% CI, 0.12-0.39 (Rebbeck, *et al.,* 2009).

Table 8.10: GRADE Profile: The level of risk of future primary breast cancer at which, and the circumstances under which, the option of risk-reducing surgery should be discussed

Quality assessment						
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**
Breast Cancer Incidence						
Lostumbo, 2010 (7 studies[1]); Domchek, 2010; Evans, 2009; Kaas, 2010						
10	observational studies	Serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	VERY LOW
Overall Survival						
Lostumbo, 2010 (4 studies); Boughey, 2010						
5	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	VERY LOW
Health related Quality of Life						
Lostumbo, *et al.*,, 2010						
17	observational studies	very serious[5]	Serious[6]	Serious[7]	very serious[8]	VERY LOW
Ovarian Cancer Incidence						
0	No Evidence Available					

[1]Lostumbo *et al.,* (2010) is a Cochrane Review including 39 studies of which only 7 were relevant to this outcome
[2] All case series studies with no standardised time points for assessing the incidence of breast cancer.
[3] All case series studies with different follow-up times and small numbers of patients
[4] Small numbers of patients in each studies (total n from 4 studies = 246)
[5]None of the included studies were designed with the specific aim of assessing quality of life outcomes
[6]There was heterogeneity across the individual studies in relation to methodologies used to assess health related quality of life
[7]Not all studies reporting quality of life included relevant populations however due to the way in which the results were reported, it was not possible to separate the relevant studies only
[8]Due to the heterogeneity in methodologies of assessment of the quality of life outcome it was felt that the results should be considered with caution and as such the decision was made to downgrade for imprecision.

Table 8.11 GRADE Profile: The level of risk of future primary breast cancer at which, and the circumstances under which, the option of risk-reducing surgery should be discussed

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Risk-reducing bilateral salpingo oophorectomy	control	Relative (95% CI)	Absolute	Quality
Overall Survival											
0	no evidence available										
Gynaecological Cancer Incidence Rebbeck, *et al.*, 2009 (3 studies)											
3	observational studies	serious[1]	no serious inconsistency	serious[2,3]	serious[4]	none			HR 0.21 (0.12 to 00.39)		VERY LOW
Breast cancer incidence Rebbeck, *et al.*, 2009 (3 studies); Metcalfe, *et al.*, 2011											
4	observational studies	serious[1]	no serious inconsistency	serious[2,3]	serious[5]	none			HR 0.49 (0.37 to 0.65)		VERY LOW

[1] All studies were case series studies with variations in methodology including follow-up times and there were some questions around whether all the populations in each study overlapped.
[2] Some studies included *BRCA* carriers who did not have a diagnosis of breast cancer
[3] *BRCA* carriers do not constitute the whole 'at risk' population
[4] The total number of patients was large (n=2840) but there were questions around whether the statistical methods were applied as stated as the systematic review, labelled forest plots as relative risks and states in methodology section that relative risks were calculate yet reports hazards ratios

Cost effectiveness evidence (2013)

A literature review of published cost-effectiveness analysis did not identify any relevant papers. No further health economic analysis was undertaken as the analysis undertaken for what carrier probability genetic testing should be offered (section 6.3) would, as a by-product, assess treatment consequences including surgery.

Recommendations

Counselling

- Refer women with a personal history of breast cancer who wish to consider risk-reducing surgery for appropriate genetic and psychological counselling before surgery. **[new 2013]**

Risk-reducing mastectomy

- Discuss the risks and benefits of risk-reducing mastectomy with women with a known or suspected of having a *BRCA1*, *BRCA2* or *TP53* mutation. **[new 2013]**
- For a woman considering risk-reducing mastectomy include in the discussion of risks and benefits:
  - the likely prognosis of their breast cancer, including their risk of developing a distal recurrence of their previous breast cancer
  - a clear quantification of the risk of developing breast cancer in the other breast
  - the potential negative impact of mastectomy on body image and sexuality
  - the very different appearance and feel of the breasts after reconstructive surgery
  - the potential benefits of reducing the risk in the other breast and relieving the anxiety about developing breast cancer. **[new 2013]**
- Give all women considering a risk-reducing mastectomy the opportunity to discuss their options for breast reconstruction (immediate and delayed) with a member of a surgical team with specialist skills in oncoplastic surgery or breast reconstruction. **[new 2013]**
- Ensure that risk-reducing mastectomy and breast reconstruction are carried out by a surgical team with specialist skills in oncoplastic surgery and breast reconstruction. **[new 2013]**
- Offer women who have *BRCA*1, *BRCA*2 or *TP53* mutations but who decide against risk-reducing mastectomy, surveillance according to their level of risk. **[new 2013]**

Risk-reducing bilateral salpingo-oophorectomy

- Discuss the risks and benefits of risk-reducing bilateral salpingo-oophorectomy with women with a known or suspected to have a *BRCA1*, *BRCA2* or *TP53* mutation. Include in the discussion the positive effects of reducing the risk of breast and ovarian cancer and the negative effects of a surgically induced menopause. **[new 2013]**
- Defer risk-reducing bilateral salpingo-oophorectomy until women have completed their family **[new 2013]**

Linking evidence to recommendations

The aim of this topic was to identify what level of risk indicated that risk-reducing surgery is a viable option for women with a personal history and a family history of breast cancer.

The GDG considered the outcomes of incidence of breast and ovarian cancers, overall survival and health related quality of life to be the most relevant outcomes to the question. No evidence was reported on the incidence of ovarian cancer in patients undergoing risk-reducing mastectomy. No evidence was reported on overall survival or health related quality of life in patients undergoing risk-reducing bilateral salpingo-oophorectomy. The quality of the evidence was very low for all outcomes on GRADE assessment.

The GDG acknowledged the heterogeneity of the available evidence. The GDG also recognised that the evidence was varied in terms of the research methods used, the different follow up times used within the identified studies and the inclusion of some patient populations which were not relevant to the question. As a result the GDG were unable to define a particular level of risk at which risk-reducing surgery should be recommended. Given this, the GDG agreed it was important, based on their clinical opinion, for women considering risk-reducing surgery to receive information on all the risks and benefits of this surgery, to aid them in making an informed decision. The GDG also noted that several of the recommendations from the previous guidance on referral for genetic and psychological counselling before surgery, opportunity to discuss options for breast reconstruction and who should carry out risk-reducing mastectomy were also relevant to women with a personal history and a family history of breast cancer. They therefore agreed to adopt these recommendations.

The GDG noted that no relevant published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The opinion of the GDG was that there may be potential additional costs associated with increased number of women being presented with the option of risk-reducing surgery. However, the GDG noted that there may also be cost savings as a result of fewer diagnoses of breast cancer and the potential reduction in screening.

The GDG also acknowledged that there are currently very limited data available to assess the survival benefits of risk-reducing surgery. It was the opinion of the GDG that recommending risk-reducing surgery could have a potential psychological impact on women particularly those issues related to body image. Conversely, having risk-reducing surgery could improve a woman's' overall survival and quality of life. Therefore the GDG decided to recommend further research in this area in order to try and monitor the outcomes of women who chose to have/chose not to have risk-reducing surgery.

Research recommendation

- Further research is recommended to compare psychosocial and clinical outcomes in women who chose and women who do not choose to have risk-reducing surgery. **[new 2013]**

8.3.5 Contra-indications to risk-reducing surgery for people with a personal history of breast cancer.

Bilateral mastectomy and/or removal of ovaries and fallopian tubes can reduce the risk of breast cancer, ovarian and fallopian tube cancers. The aim of risk-reducing surgery is to prevent a future new primary cancer. There are however, risks associated with risk-reducing surgery and there are circumstances when risk-reducing surgery would be inadvisable. Such circumstances include patients with co-morbidities that either significantly increase the risk of complications of surgery or where the prognosis from the current cancer is poor and the person is unlikely to benefit. Other circumstances may be relevant to consider, for example

women keen to have children would advised against removal of ovaries until they have completed their family.

Clinical Question: What are the factors that indicate that offering risk-reducing surgery is not appropriate?

Clinical Evidence (new 2013) (see also full evidence review)

Evidence Statements

There is conflicting very low quality evidence about the relationship between age and outcome following contralateral prophylactic mastectomy in women diagnosed with breast cancer (Tercyak, *et al.,*,, 2007; Montgomery, *et al.,* 1999 and Graves, *et al.,* 2007; Table 8.12). Two studies did not find a difference in the quality of life of younger and older patients following contralateral prophylactic mastectomy (Tercyak, *et al.,* 2007; Montgomery *et al.,*, 1999) whereas younger age was associated with general distress in Graves, *et al.,* (2007).

Literature searches identified no evidence about the relationship between parity, menopausal status, comorbidity, patient choice, life expectancy, metastatic and quality of life following contralateral prophylactic mastectomy.

Table 8.12: GRADE Profile: The factors which indicate that offering risk-reducing surgery is not appropriate

Quality assessment							Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	
Quality of Life							
3	observational studies	serious[1]	very serious[2]	serious[3]	serious[4]	none	VERY LOW

[1] All studies were case series studies and were not primarily designed to assess quality of life in the patients participating.
[2] Three studies provide conflicting evidence that age is related to quality of life outcomes. The conflict in the results may be due to the fact that the three studies compared different age groups and used different assessments of quality of life/distress.
[3] None of the studies were designed to assess the impact of the various factors listed in the PICO on quality of life or on patient satisfaction.
[4] All included studies had small numbers of patients and in at least one case there was a high risk of selection bias due to the method of recruitment used, all of which will have and impact on the precision of the results presented.

Cost effectiveness evidence (2013)

A literature review of published cost-effectiveness analysis did not identify any relevant papers. No further health economic analysis was undertaken as this topic was not relevant for modelling.

Recommendations

- Do not offer risk-reducing surgery to people with co-morbidities that would considerably increase the risks of surgery. **[new 2013]**
- Do not offer risk-reducing surgery to people who have a limited life expectancy from their cancer or other conditions**. [new 2013]**

Linking evidence to recommendations

The aim of this topic was to identify what factors indicate that offering risk-reducing surgery is not appropriate to people with a personal history and a family history of breast cancer.

The GDG considered the outcomes of health related quality of life and patient satisfaction to be the most relevant to this question. No evidence was reported for the outcome of patient satisfaction. The quality of the evidence was very low for the reported outcome on GRADE assessment.

The GDG acknowledged that the evidence consisted of case series studies with very small populations. In at least one study there was a high risk of selection bias due to the method of recruitment used. Methods of assessing quality of life differed across the individual studies and therefore it was not possible to perform direct comparisons between studies. The GDG also noted that the included studies were not primarily designed to assess quality of life issues. Given these limitations the GDG also used their clinical experience to help determine which factors would indicated risk-reducing surgery was not appropriate.

It was the opinion of the GDG that not performing risk-reducing surgery in people with co-morbidities or a limited life expectancy from cancer or other conditions could reduce unnecessary surgical procedures in people who are unwell are unlikely to gain any benefit or run a significant risk of harm from the surgery.

A literature review of published cost-effectiveness analyses identified three potentially relevant papers. However, these papers were excluded as the population focused on women without breast cancer. The GDG noted that no additional economic analysis had been undertaken in this area. The GDG noted that there may be potential cost savings from a possible reduction in unnecessary surgery.

Therefore the GDG recommended that risk-reducing surgery should not be offered to people with a limited life expectancy from their cancer or other conditions or co-morbidities that increase the risks associated with surgery.

8.4 Radiotherapy people with a personal history of breast cancer who are *TP53* mutation carriers

There is concern that *TP53* gene mutation carriers are at increased risk of developing radiation induced cancers. For this group of people it is particularly important to consider the risks and benefits of breast conserving surgery followed by radiotherapy versus mastectomy as part of their breast cancer treatment.

Clinical Question: What is the effectiveness of mastectomy compared with breast conserving surgery plus radiotherapy for people with newly diagnosed breast cancer including high-grade ductal carcinoma in situ (DCIS) with a *TP53* mutation or at high risk of *TP53* mutation?

Clinical Evidence (2013] (see also full evidence review)

Evidence Statements

There was no evidence about the effectiveness of mastectomy compared to breast conserving surgery plus radiotherapy in patients with a newly diagnosed breast cancer and a *TP53* mutation (or at high risk of *TP53* mutation).

Radio Induced Malignancy

Very low quality evidence suggests a significant risk of radio induced malignancy following radiotherapy for breast cancer in women with a p53 mutation. In one retrospective case series study (Heymann, *et al.,* 2010), 6 women with p53 mutation who received loco-regional radiotherapy for breast cancer were identified. There were 2 recorded cases of radio induced malignancy in this group (Table 8.13).

Table 8.13: GRADE Profile: what is the effectiveness of mastectomy compared with breast conserving surgery plus radiotherapy for people with newly diagnosed breast cancer or high grade ductal carcinoma in situ with a *TP53* mutation or at high risk of *TP53* mutation?

Quality assessment						Summary of findings				
						No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Breast conserving surgery and adjuvant radiotherapy	Mastectomy	Relative (95% CI)	Absolute	Quality
Radio Induced Malignancy (follow-up median 6 years) (Heymann, *et al.*,, 2010)										
1	observational studies	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[3]	2/6 (33.3%)	0/2 (0%)	not pooled	not pooled	VERY LOW
							0%		not pooled	

[1] Only 8 patients in the study, though this is possibly due to the fact that this topic is investigating an extremely rare event and therefore large randomised trials are unlikely to be possible.
[2]There are not enough data or studies to comment on the consistency with any certainty
[3] There are only 8 patients included in the study and all 8 patients received different treatment plans, though only the effects of radiotherapy and incidence of radio-induced malignancies are of interest to this topic.

Cost effectiveness evidence (2013)

A literature review of published cost-effectiveness analysis did not identify any relevant papers. No further health economic analysis was undertaken as the rarity of the diagnosis and resulting small number of people affected are unlikely to have large impacts on NHS budgets.

Recommendations

- When a person has invasive breast cancer or ductal carcinoma in situ and is known to have a *TP53* mutation or at high likelihood of a *TP53* mutation:
  - inform them of all the possible treatment options
  - make sure they know about the uncertainties associated with these treatment options
  - inform them of the risks associated with each treatment (for example, the risk of recurrence, the risk of new primary breast cancer and the risks of malignancy associated with radiotherapy and chemotherapy). **[new 2013]**
- Offer people with invasive breast cancer or ductal carcinoma in situ and a high likelihood of a *TP53* mutation, genetic testing to help determine their treatment options. **[new 2013]**

Linking Evidence to Recommendations

The aim of this topic was to identify the effectiveness of mastectomy compared with breast conserving surgery, plus radiotherapy for people with newly diagnosed breast cancer including high grade ductal carcinoma in situ (DCIS) with a *TP53* mutation or at high risk of a *TP53* mutation.

The GDG considered the outcomes of overall survival, recurrence, quality of surgery, health related quality of life and new primary cancer to be the most clinically relevant to this question. None of the outcomes were reported in the evidence. An additional outcome of radiation induced malignancy was therefore considered by the GDG. The quality of the evidence was very low for this outcome on GRADE assessment.

The GDG noted that the majority of published evidence reported somatic mutations in *TP53* and was therefore not relevant to this question. The GDG therefore agreed to base their discussion on a single paper that reported on patients with germline *TP53* mutations. Due to the limited evidence available the GDG were not able to make recommendations on the most effective treatment for this group of people.

The GDG agreed that there was uncertainty over the most effective treatment for people with either a known *TP53* mutation or who were at high risk of carrying a *TP53* mutation. Given this uncertainty, the GDG felt, based on their clinical experience, that giving information on treatment options could potentially cause psychological harm. However, the GDG agreed that guiding healthcare professionals to provide balanced information on the potential treatment options, including the uncertainties and risks associated with them, would assist patients with making informed decisions.

The GDG noted that no relevant published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The opinion of the GDG, based on their clinical experience was that provision of information would not incur any additional costs or any cost savings.

Given the lack of data available to inform a recommendation on the most effective treatment option for this group of people, the GDG agreed that further research in this area would be beneficial. However, since a *TP53* mutation is a rare diagnosis, the GDG did not believe it was practical to recommend RCT research. They therefore recommended that international collaborative studies were undertaken to assess the risks of radiotherapy and chemotherapy for people with a *TP53* mutation.

Research recommendation

- Prospective and retrospective international collaborative studies are recommended to assess the risks and benefits of radiotherapy and chemotherapy for people with a *TP53* mutation.**[new 2013]**

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Appendix A

Abbreviations

ATM	Ataxia Telangectasia Mutated
BRCA1	BReastCAncer 1 gene
BRCA2	BReastCAncer 2 gene
HRT	Hormone Replacement Therapy
MDT	Multi-Disciplinary Team
NPV	Negative Predictive Value
PPV	Positive Predictive Value
PTEN	Protein on chromosome TEN

Appendix B

Glossary

Absolute Risk
The absolute risk of an event is the probability of that event occurring. Absolute risks may be specified over a specific time period. For example:

- the lifetime risk of a disease is the probability of that risk developing during the lifetime.
- the 10-year risk of a disease is the probability of developing the disease within ten years.
- the Absolute risk by age 70 is the probability of developing the disease by age 70.

Adverse Event
Detrimental change in health, or side effect, occurring in a patient receiving the treatment.

Adverse Clinical Outcome
Detrimental change in health that occurs in a patient.

Age-specific risk
The estimated risk of developing the disease in the next year based on a specific age or age band. Five or ten year age bands are typically used.

Adjuvant therapy
Treatment given after surgery, generally designed to remove any microscopic traces of tumour which may have been left behind.

Aromatase inhibitors
Drugs that reduce the blood levels of oestrogen in postmenopausal women by blocking aromatase, a key enzyme which helps to form oestrogen from other steroids.

Bilateral
Both sides, i.e. both breasts or both ovaries.

Bilateral breast cancer
Cancer that occurs in both breasts.

Bilateral Salpingo-Oophorectomy
The surgical removal of both ovaries and both fallopian tubes.

Breast conserving surgery
Surgery in which the cancer is removed, together with a margin of normal breast tissue. The whole breast is not removed.

Breast density
Density of breast tissue, usually referring to mammographic appearance.

Breast reconstruction
The formation of a breast shape after a total mastectomy, using a synthetic implant or tissue from the woman's body.

Cancer centre
Cancer services are based in cancer centres. Such centres provide the entire spectrum of cancer care – both on-site and to associated cancer units

Carcinoma
Cancer of the lining tissue that covers all the body organs.

Care plan
A document which details the care and treatment that a patient/user receives and identifies who delivers the care and treatment.

Chemotherapy
The use of medication (drugs) that are toxic to cancer cells, given with the aim of killing the cells or preventing or slowing their growth.

Clinical effectiveness
The extent to which an intervention produces an overall health benefit in routine clinical practice.

Clinical Question
This term is sometimes used in guideline development work to refer to the questions about treatment and care that are formulated in order to guide the search for research evidence. When a clinical question is formulated in a precise way, it is called a focused question.

Clinical Population
A group of people that are studied for health reasons.

Clinically Relevant
An outcome or event which has a direct relevance to a patient's health status, or which is important in modifying which treatment is received or how it is delivered.

Cohort studies
Observational studies in which outcomes are compared in a group of individuals "exposed" to a factor of interest with a similar group of people who are "not exposed".

Contraindicated
A situation in which a medication or treatment should not be administered.

Contralateral breast cancer
Cancer in the opposite breast.

Cost Benefit Analysis
A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.

Cost Effectiveness Analysis
A type of economic evaluation comparing the costs and the effects on health of different treatments. Health effects are measured in health-related units, for example the cost of preventing one additional heart attack.

Cost Effectiveness
Value for money. A specific healthcare treatment is said to be cost effective if it gives a greater health gain than could be achieved by using the resources in other ways.

Cost-effectiveness model
An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.

Cumulative risk
The absolute risk, or probability of an event occurring over a specified time period.

Dominance
An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective.

Ductal carcinoma in situ (DCIS)
The commonest form of preinvasive breast cancer, which is confined to the breast epithelium and has not infiltrated the basement membrane into the supporting breast tissue and thus cannot have spread to other sites in the body.

EQ-5D (EuroQol-5D)
A standardised instrument used to measure a health outcome. It provides a single index value for health status.

Evidence Table
A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.

Extrapolation
In data analysis, predicting the value of a parameter outside the range of observed values.

False negative
A result that appears negative but should have been positive, i.e. a test failure

False positive
A result that appears positive but should have been negative, i.e. a test failure.

Family History
A family history of disease in an individual is the occurrence of the disease in a blood relative of that individual.

Gene
A gene is a molecular unit of heredity of a living organism.

Genetic Counselling
The process by which individuals or families, at risk of an inherited disorder are advised of the consequences and nature of the disorder, the probability of developing or transmitting it, and the options open to them.

Genetic Counsellor
A healthcare professional providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. If it is appropriate, they will discuss genetic testing, coordinate any testing, interpret test results, and review all additional testing, surveillance, surgical, or research options that are available to members of the family.

GP
General Practitioner.

GRADE
The GRADE approach is a method of grading the quality of evidence and strength of recommendations in healthcare guidelines. It is developed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group.

Heterogeneity
A term used to describe the amount of difference of results or effects.

Homogeneity
A term used to describe the amount of similarity of results or effects.

Hormone receptor
Proteins on or in a cell that bind to specific hormones.

Hormone replacement therapy
Supplements to replace the normal female hormone (oestrogen and progesterone) after a natural menopause (the stopping of periods) or induced menopause (removal of the ovaries often at the time of a hysterectomy).

Incremental analysis
The analysis of additional costs and additional clinical outcomes with different interventions.

Incremental cost
The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.

Incremental cost-effectiveness ratio (ICER)
The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.

Incremental net benefit (INB)
The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.

Imaging
The production of images of organs or tissues using radiological procedures, e.g. x-rays, ultrasound and MRI scans.

Investigation
A medical procedure to assist diagnosis.

Ipsilateral
On, or affecting, the same side.

Magnetic resonance imaging (MRI)
A diagnostic imaging technique that uses powerful electromagnets, radio waves and a computer to produce well-defined images of the body's internal structures.

Mammography
The process of taking a mammogram.

Mammogram
A soft tissue x-ray of the breast which may be used to evaluate a lump or which may be used as a screening test in women with no signs or symptoms of breast cancer.

Markov model
A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).

Mastectomy
An operation aiming to remove breast tissue. When the operation is performed on both breasts it is bilateral. There are three different types of mastectomy:

- Simple Mastectomy aims to remove all of the breast. This includes the breast tissue and the nipple and surrounding areola.
- Subcutaneous Mastectomy removes the majority of the breast tissue but leaves the nipple and areola and some underlying breast tissue.
- Skin sparing mastectomy removes the majority of the breast tissue and the nipple and areola.

Medical oophorectomy
Hormone therapy to stop the functioning of the ovaries.

Meta-analysis
A method of summarizing previous research by reviewing and combining the results of a number of different clinical trials or studies.

Menopause
The end of menstruation; this usually occurs naturally around the age of 50, but maybe induced surgically by the removal of the ovaries (bilateral oophorectomy).

Mixed Treatment Comparisons
A type of meta-analysis which allows simultaneous comparisons of greater than two treatment options.

National Breast Screening Programmes
Breast screening looks for breast cancer before symptoms show, which involves taking x-rays (mammograms) of the breast. The following programmes are available in the UK:

- 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)

Odds ratio
A measure of treatment effectiveness. The odds of an event happening in the intervention group, divided by the odds of it happening in the control group. The 'odds' is the ratio of non-events to events.

Oestrogen
A female sex hormone.

Oncoplastic
Cancer specific reconstructive surgery.

One-way simple sensitivity analysis (univariate analysis)
Each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study.

Oophorectomy
The surgical removal of an ovary.

Opportunity cost
The loss of other health care programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.

Osteoporosis
The loss of bony tissue resulting in bones that are brittle and liable to fracture.

Predictive values/markers
A molecule that is assessed to predict the likely response to a specific treatment, for example oestrogen receptor to predict the likely response to endocrine therapy.

Primary care
Services provided in a community setting, outside secondary care, with which patients usually have first contact.

Primary tumour
Original site of the first cancer.

Probabilistic sensitivity analysis
Probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques.

Progesterone receptor
A protein within cells that binds to progesterones.

Prognosis
A prediction of the likely outcome or course of a disease; the chance of recovery, recurrence or death.

Prognostic factors
Patient or disease characteristics, e.g. age, or co-morbidity, that influence the course of the disease under study

Prognostic study
A study that examines selected predictive variables, or risk factors, and assesses their influence on the outcome of a disease.

Prophylaxis
The prevention of disease; preventive treatment. Interventions to prevent an unwanted outcome.

Prospective diagnostic study
A study that looks at a new diagnostic method to see if it is as good as the current 'gold standard' method of diagnosing a disease.

Prospective Study
A study in which people are entered into research and then followed up over a period of time with future events recorded as they happen

Psychological
Adjective of psychology, which is the scientific study of behaviour and its related mental process. Psychology is concerned with such matters as memory, rational and irrational thought, intelligence, learning, personality, perceptions and emotions and their relationship to behaviour.

Psychosocial
Concerned with psychological influences on social behaviour.

Publication bias
Also known as reporting bias. A bias caused by only a subset of all the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (e.g. only outcomes or sub-groups where a statistically significant difference was found.

Qualitative Study
A study used to explore and understand peoples' beliefs, experiences, attitudes, behaviour and interactions.

Quality adjusted life years (QALYs)
A measure of health outcome which looks at both length of life and quality of life. QALYS are calculated by estimating the years of life remaining for a patient following a particular care pathway and weighting each year with a quality of life score (on a 0 to 1 scale). One QALY is equal to 1 year of life in perfect health, or 2 years at 50% health, and so on

Raloxifene
Used for the prevention of osteoporosis in postmenopausal women and for the reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis.

Radiotherapy
A treatment for cancer that uses high energy ionising radiation to kill cells.

Randomised controlled trials (RCTs)
A clinical trial in which subjects are randomised to different groups for the purpose of studying the effect of a new intervention, for example a drug or other therapy.

Relative risk (also known as risk ratio)
The ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability or rate) is the ratio of people with an event in a group to the total in the group. A relative risk (RR) of 1 indicates no difference between comparison groups. For undesirable outcomes, an RR that is less than 1 indicates that the intervention was effective in reducing the risk of that outcome.

Relatives - First-degree relatives
These are the closest blood relatives (relatives by marriage do not count). These include father, mother, son, daughter, brother, sister. They are on both the mother and father's side of the family.

Relatives – Second-degree relatives
These are blood related grandparents, grandchildren, uncle, aunt, first cousin, nephew and niece. They are on both the mother and father's side of the family.

Relatives - Third-degree relatives
These are blood related great grandparents, great grandchildren, great uncle, great aunt, children of great uncle or great aunt, second first cousin, children of first cousin, grand nephew and grand niece. They are on both the mother and father's side of the family.

Recurrence
Recurrence is when new cancer cells are detected following treatment. This can occur either at the site of the original tumour or at other sites in the body.

Regimen
A plan or regulated course of treatment.

Retrospective Data
Data that deals with the present/past and does not involve studying future events

Risk
Being at risk of breast cancer means that there is a possibility that the person will develop the disease, but doesn't necessarily mean that it will happen.

Risk factor
A clearly defined occurrence or characteristic that, in research studies of similar people, has been associated with the increased rate of a subsequently occurring disease or health problem. Risk factors include aspects of personal behaviour, lifestyle, environmental exposure, or inborn or inherited characteristics, which are known to be associated with the disease.

Secondary care
Services provided by multidisciplinary team in the hospital, as opposed to the General Practitioner and the primary care team.

Sensitivity
The proportion of individuals who have disease correctly identified by the study test

Sensitivity analysis
A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results.

Sentinel lymph node
The sentinel lymph node is the first lymph node that filters fluid from the breast. This is usually found in the lower part of the armpit.

Specialist
Person who is an expert in the subject.

Specificity
The proportion of individuals who do not have a disease and who are correctly identified by the study test.

Structural sensitivity analysis
Different structures of economic model are used to test the impact of model structure on the results of the study.

Systematic review
A systematic review of the literature carried out to answer a defined question often using quantitative methods to summarise the results.

Tamoxifen
Adjuvant treatment for oestrogen-receptor positive early breast cancer and also for the treatment of oestrogen-receptor positive locally advanced or metastatic breast cancer

Time horizon
The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.

Trial or Clinical Trial
Research study conducted with patients, usually to evaluate a new treatment or drug. Each trial is designed to answer scientific questions and to find better ways to treat individuals with a specific disease.

True negative
When testing for a condition or disease, this result confirms the absence of the condition in an individual who genuinely does not have the condition in question. (Contrast with false negative (see above) where the test may incorrectly indicate that the individual is free from the condition being investigated. The condition is present but not detected by the test.).

True positive
When testing for a condition or disease, this result confirms the presence of the condition in question in individuals who have it. (Compare with false positive where the test may incorrectly indicate that the individual has a condition, but in fact they do not.)

Ultrasound
An imaging method in which high-frequency sound waves are used to outline a part of the body.

Utility

A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value

Wide local excision

The complete removal of a tumour with a surrounding margin of normal breast tissue.

X-ray

An imaging technique that uses energy beams of very short wavelengths that can penetrate most substances except heavy metals. This is the most common form of imaging technique used in clinical practice everywhere in the world, with the image captured on photographic film.

Appendix C

Guideline scope

C1 Guideline scope 2004 (the 2006 update used the scope from the 2004 guideline)
C2 Guideline scope 2013

Appendix C1

Guideline Scope (2004)

Guideline title

Familial breast cancer: classification and care of women at risk of familial breast cancer in primary, secondary care and tertiary care

Short title

Familial breast cancer

Background

a) The National Institute for Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Primary Care to develop a clinical guideline on the classification and care of women at risk of familial breast cancer for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health and Welsh Assembly Government. The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

b) The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued will have the effect of updating the Framework.

Clinical need for the guideline

a) 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. Environmental factors will also usually contribute to the development of breast cancer. Familial clustering may therefore be the result of chance, an increase in genetic susceptibility, a common lifestyle and/or environmental factors. For these women, the degree of risk of developing breast cancer varies according to the:

- nature of the family history
- number of relatives who have developed breast cancer
- age at which the relative(s) developed breast cancer
- age of the individual concerned.

b) The lifetime risk of developing breast cancer is about 11% for the British female population. Women with female relatives who have or have had breast cancer may have a higher risk. The possibility of identifying those women at increased risk has implications for the ability to prevent or reduce morbidity

The guideline

a) The guideline development process is described in detail in three booklets that are available from the NICE website (see 'Further information'). *The Guideline Development Process – Information for Stakeholders* describes how organisations can become involved in the development of a guideline.

b) This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health and Welsh Assembly Government..

c) The areas that will be addressed by the guideline are described in the following sections

Population

The guideline will include a limited epidemiological overview together with a discussion of the genetic influences in familial breast cancer.

Groups that will be covered

a) Women aged 18 years and older who may be at increased risk of developing breast cancer because of a family history of breast or ovarian cancer.

Groups that will not be covered

b) Women with diagnosed breast cancer.
c) The guideline will not refer to men, but the recommendations will be pertinent.

Healthcare setting

a) The guideline will cover the care received from primary, secondary and tertiary healthcare professionals who are involved in the care of women who present with an increased risk, real or perceived, of developing breast cancer.

b) The guideline will also be relevant to the work, but will not cover the practice, of those concerned with breast screening services and the identification of ovarian cancer.

Clinical management

The guideline will include recommendations on the following areas.

a) Assessment of risk of breast cancer, including the need for genetic tests and the interpretation of the results.

b) Cascade testing, or surveillance, for women at increased risk.

c) Classification and care of women at risk of familial breast cancer in breast cancer screening programmes. (See note in [d] on recommendations regarding the use of pharmacological interventions.)

d) Management plans including psychological support. Advice on treatment options will be based on the best evidence available to the Guideline Development Group. When referring to pharmacological treatments, the guideline will normally recommend use within the licensed indications. Exceptionally, and only where the evidence supports

it, the guideline may recommend use outside the licensed indications. The guideline will expect that prescribers will use the Summary of Product Characteristics to inform their prescribing decisions for individual patients.

e) Referral.

f) Patient/family/carer information and support. Women covered by this guideline include family members who are concerned they may be at increased risk of familial breast cancer.

Audit support within guideline

The guideline will be accompanied by level 2 audit review criteria and advice

Related NICE guidance

Completed appraisals

National Institute for Clinical Excellence (2003) Guidance on the use of capecitabine for the treatment of locally advanced or metastatic breast cancer NICE Technology Appraisal Guidance No. 62. London: National Institute for Clinical Excellence.

National Institute for Clinical Excellence (2001) Guidance on the use of taxanes for the treatment of breast cancer. NICE Technology Appraisal Guidance No. 30. London: National Institute for Clinical Excellence.

National Institute for Clinical Excellence (2002) Guidance on the use of trastuzumab for the treatment of advanced breast cancer. NICE Technology Appraisal Guidance No. 34. London: National Institute for Clinical Excellence.

Completed Cancer service guidance

National Institute for Clinical Excellence (2002) Guidance on Cancer Services Improving Outcomes in Breast Cancer: Manual Update London: National Institute for Clinical Excellence

Appraisals In progress

Vinorelbine for breast cancer (expected date of issue, September 2002)

Guideline and service guidance in progress

Supportive and palliative care for people with cancer - service guidance (expected date of issue, Autumn 2003)

Referral guidelines for suspected cancer (expected date of issue, Spring 2005)

Appendix C2

Guideline Scope (2013)

Guideline title

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

Short title

Familial breast cancer

The remit

The National Collaborating Centre for Cancer has been commissioned by NICE to partially update 'Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care', NICE clinical guideline 41 (2006), available from www.nice.org.uk/guidance/CG41. See section 4.3.1 of this scope for details of which sections will be updated. Sections 4.3.1 a and b of the update will include men. We will also carry out an editorial review of all recommendations to ensure that they comply with NICE's duties under equalities legislation. This update is being undertaken as part of the guideline review cycle.
The Department of Health has also asked NICE to produce a short clinical guideline on the management of breast cancer in women and men who have a family history of breast cancer[35].

Clinical need for the guideline

Epidemiology

Familial breast cancer typically occurs in people with an unusually high number of family members affected by breast, ovarian or a related cancer. If more cases of breast, ovarian or a related cancer are seen in a family than would be expected by chance alone, this can be a sign that genes have caused or contributed to its development. Environmental factors also contribute to the development of breast cancer, so familial clustering may be the result of chance, increased genetic susceptibility, lifestyle or common environmental factors.

For people with a family history of breast, ovarian or a related cancer, the risk of developing breast cancer depends on the:

- nature of the family history
- number of relatives who have developed breast, ovarian or a related cancer
- age at which relatives developed breast cancer
- age of the person.

In the UK, the lifetime risk of developing breast cancer is about 11–12.5% for a woman, and less than 0.1% for a man. People with relatives who have, or have had breast, ovarian or a

[35] This remit has not been finalised and is subject to ministerial agreement.

related cancer might have a higher risk than the general population. Identifying people at increased risk could prevent or reduce morbidity.
Breast cancer in people who have a family history of breast, ovarian or a related cancer may need different management from that in people without a family history of these cancers. This is because of differences in the future risk of developing contralateral breast cancer (that is, cancer in the other breast) or, in women of developing ovarian cancer.

Current practice

Classification and care of women at risk of familial breast cancer

Implementation of NICE clinical guideline 41 has been patchy. Genetic testing for *BRCA1* and *BRCA2* mutations is still largely driven by the finding of a *BRCA1* or *BRCA2* mutation in a family member with breast or ovarian cancer.

The threshold for testing has decreased from a 20% likelihood of *BRCA1* or *BRCA2* mutation to 10% in many centres. Testing is now offered at lower thresholds because high throughput and more rapid testing is available. This has led to questions about whether testing thresholds should be lowered and whether unaffected women at very high risk of *BRCA1* or *BRCA2* mutation should have access to testing even if an affected family member is unavailable for testing.

The use of tamoxifen and raloxifene as preventive drugs is increasing, especially in North America, but use in England and Wales is limited because there is no European marketing authorisation for preventive use at present.

Women without breast cancer who have *BRCA1* or *BRCA2* mutations and have early bilateral salpingo-oophorectomy (removal of both ovaries and fallopian tubes) tend not to use hormone replacement treatment (HRT) and may be encouraged not to take HRT by their clinicians. New evidence suggests that these women should take HRT until around 50 years of age to reduce their risk of cardiovascular disease and osteoporosis because use in this situation does not appear to negate the protective effect of a bilateral salpingo-oophorectomy on breast cancer risk.

Management of breast cancer and related risks in people with a family history of breast cancer

The risk of further primary breast tumours (that is, a second tumour in the contralateral [previously unaffected] breast that is not related to the first one) in people with breast cancer and a family history of breast, ovarian cancer or a related cancer means that options for ongoing surveillance and risk-reducing surgery could differ from those recommended in 'Early and locally advanced breast cancer: diagnosis and treatment', NICE clinical guideline 80 (2009).

Current practice in the UK varies considerably as to whether the risk of second primary tumours is discussed or whether risk-reducing surgery (contralateral mastectomy, bilateral salpingo-oophorectomy or both) is presented as a realistic primary treatment option to people newly diagnosed with invasive breast cancer, or as a delayed option. Genetic testing at the time of diagnosis is used across North America and Europe, but is very rare in the UK.

Improvements in genetic testing now make testing at the time of diagnosis an option that people could use to inform their decisions about treatment. In particular, it may be better for women at high risk of, or who have, a *TP53* mutation to be offered mastectomy rather than conservative surgery and radiotherapy. Early identification of cases of familial breast cancer may allow surgical, radiotherapy and systemic treatments to be altered to improve outcomes.

Need for guidance

There is a need to update the recommendations in NICE clinical guideline 41 on genetic testing thresholds, surveillance and use of preventive therapies for people without breast cancer who are at increased risk because of a family history of breast, ovarian or a related cancer. For those recommendations in NICE clinical guideline 41 that are not being updated, the GDG will be asked to carry out an editorial review to ensure that they comply with NICE's duties under equalities legislation (for example, to determine whether the recommendations made for women in the original guideline are also applicable to men).

For people with a diagnosis of breast cancer and a family history of breast, ovarian or a related cancer new guidance is needed to fill the gaps between NICE clinical guidelines 41 and 80 to address differences in management of breast cancer at diagnosis and in subsequent surveillance.

The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health. The areas that will be addressed by the guideline are described in the following sections.

Population

Groups that will be covered

Classification and care of women at risk of familial breast cancer (update)

- Adult women (18 years and older) without breast cancer who may be at increased risk of developing breast cancer because of a family history of breast, ovarian or a related cancer.
- Adult men (18 years and older) without breast cancer who may be at increased risk of developing breast cancer because of a family history of breast, ovarian or a related cancer, for the consideration of risk thresholds for testing only (see 4.3.1 a and b).
- Specific consideration will be given to the needs of people from groups with a particularly high prevalence of *BRCA1* or *BRCA2* mutations, such as people of Jewish origin.

Management of breast cancer and other risks in people with a family history of breast cancer

- Adult women and men (18 years and older) with a recent diagnosis of breast cancer and a family history of breast, ovarian or a related cancer.
- Specific consideration will be given to the needs of people from groups with a particularly high prevalence of *BRCA1* or *BRCA2* mutations, such as people of Jewish origin.

Groups that will not be covered

Classification and care of women at risk of familial breast cancer (update)

- Children (younger than 18).
- Men, except for the consideration of risk thresholds for testing

Management of breast cancer and related risks in people with a family history of

breast cancer

- Children (younger than 18).

Healthcare setting

- All settings in which NHS care is received.

Clinical management

Key clinical issues that will be covered

Classification and care of women at risk of familial breast cancer (update)

- Assessing the risk threshold for genetic testing (for the update this part of the topic will be extended to include the threshold for testing for men as well as women).
- The risk threshold at which genetic testing should be offered to people who do not have living relatives who have had breast, ovarian or a related cancer available to test (for the update this part of the topic will be extended to include the threshold for offering testing to men as well as women).
- Chemoprevention to reduce the incidence of breast cancer in women.
- Specific surveillance needs of women with no personal history of breast cancer.
- HRT for women who have had a bilateral salpingo-oophorectomy before the natural menopause.

Management of breast cancer and other risks in people with a family history of breast cancer

- Assessing risk thresholds for genetic testing.
- The risk thresholds at which genetic testing should be offered to an affected person to:
  - inform future care
  - initiate genetic tests for their relatives.
- Genetic testing for *BRCA1 BRCA2* and *TP53* within 4 weeks of diagnosis of breast cancer to inform treatment and future surveillance:
  - Does a delay in genetic testing at diagnosis affect outcome?
  - Who should discuss the outcomes of genetic testing with the patient and when?
- Risk-reducing breast or ovarian surgery:
  - At what level of risk of future primary breast cancer, and in what circumstances, should the option of risk-reducing surgery be discussed?
  - In what circumstances is offering risk-reducing surgery not appropriate?
- The specific surveillance needs of people with a personal history of breast cancer.
- Mastectomy compared with breast-conserving surgery plus radiotherapy for people with newly diagnosed breast cancer or high-grade ductal carcinoma in situ with a *TP53* mutation or at high risk of a *TP53* mutation.

Main outcomes

- Incidence of familial breast cancer.
- Mortality from breast cancer.
- Health related quality of life.

Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually only be from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see 'Further information').

Status

Scope

This is the final scope.

Timing

The development of the guideline recommendations will begin in July 2011.

Related NICE guidance

Published guidance

NICE guidance to be updated

This guideline will update and replace the following NICE guidance.

- Familial breast cancer. NICE clinical guideline 41 (2006). Available from www.nice.org.uk/guidance/CG41

Other related NICE guidance

- Advanced breast cancer. NICE clinical guideline 81 (2009). Available from www.nice.org.uk/guidance/CG81
- Breast cancer (early and locally advanced). NICE clinical guideline 80 (2009). Available from www.nice.org.uk/guidance/CG80
- Improving outcomes in breast cancer. NICE cancer service guidance CSGBC (2002). Available from www.nice.org.uk/guidance/CSGBC

Further information

Information on the guideline development process is provided in:

- 'How NICE clinical guidelines are developed: an overview for stakeholders' the public and the NHS'
- 'The guidelines manual'.

These are available from the NICE website (www.nice.org.uk/guidelinesmanual). Information on the progress of the guideline will also be available from the NICE website (www.nice.org.uk).

Appendix D

People and organisations involved in the production of the guideline

D1 Members of the 2013 Guideline Development Group

D2 Members of the 2004 Guideline Development Group

D3 Members of the 2006 Guideline Development Group

D4 Organisations invited to comment on the guideline [2013]

D5 Individuals carrying out literature reviews and complementary work [2013]

D6 Members of the NICE project team [2013]

Appendix D1

Members of the 2013 Guideline Development Group

GDG Chair

Ms Maggie Alexander	Director of Policy and Campaigns, Breakthrough Breast Cancer, London

GDG Lead Clinician

Professor Gareth Evans	Consultant Clinical Geneticist, St Mary's Hospital, Manchester

Group Members

Miss Amanda Taylor	Consultant Surgeon, Milton Keynes NHS Trust
Dr Nadeem Qureshi	Clinical Reader in Primary Care, University of Nottingham
Dr Andrew Cuthbert	Cancer Genetic Counsellor, Birmingham Women's Healthcare Trust
Professor Anneke Lucassen	Professor of Clinical Genetics, Consultant in Clinical Genetics, University of Southampton/Wessex Clinical Genetics Service
Professor Diana Eccles	Professor of Clinical Genetics, Wessex Clinical Genetics Service
Professor Fiona Gilbert	Professor or Radiology, University of Cambridge
Dr Anne Armstrong	Consultant Medical Oncologist, The Christie NHS Foundation Trust, Manchester
Mrs Susan Heard	Nurse Practitioner in Breast Care, Park Breast Unit, Brighton
Professor Paul Pharaoh	Professor of Cancer Epidemiology, University of Cambridge
Dr Nina Hallowell	Programme Lead, PHG Foundation, Strangeways Laboratories, Cambridge
Dr Ulrike Harrower	Consultant in Public Health, NHS Somerset
Dr Kathie Binysh	Medical Director, North West London Cancer Network
Mrs Ursula Van Mann	Patient and carer member
Mrs Wendy Watson	Patient and carer member
Dr Caitlin Palframan	Patient and carer member

Declarations of interest

The Guideline Development Group were asked to declare any possible conflicts of interest which could interfere with their work on the guideline. The interests that were declared are as follows:

GDG Member	Interest Declared	Type of Interest	Decisions Taken
Gareth Evans	Department received payment from Astra Zeneca for sending tumour tissue samples on BRCA1/2 Carriers to be used in research for PARP inhibitors	Non Personal Pecuniary Non-specific	Declare and can participate in discussions on all topics as PARP inhibitors are not being investigated by the guideline.
	Principal investigator of FH02 screening trial which evaluates mammography aged 35-40 years for familial breast cancer, Funded by Breast Cancer Campaign. Department receives funding	Non Personal Pecuniary Specific	Declare and can participate in discussions on all topics as not funded by health industry.
	Co-Author on paper published in August 2012 regarding *BRCA* carriers, prophylactic salpingo-oophorectomy and menopause: clinical management considerations and recommendations for Future Science Group, Women's Health	Personal Non-Pecuniary	Declare and withdraw from drafting recommendations in hormonal replacement therapy and risk-reducing surgery from September 2012. In GDG meetings after September 2012 only editorial changes to recommendations on these topics were discussed.
Nadeem Qureshi	Received an research grant to assess the implementation of familial hypercholestolamia in primary care	Non Personal Pecuniary Non-specific	Declare and can participate in discussions on all topics as subject area is not being investigated by the guideline.
	Published a paper on Primary Care research evidence underpinning NICE guideline, University received overhead costs.	Non Personal Pecuniary Non-specific	Declare and can participate in discussions on all topics as subject area is not being investigated by the guideline.
	Collaborating on an NIHR Research for Patient Benefit Grant to explore the topic of Primary Care research evidence underpinning NICE guideline.	Non Personal Pecuniary Non-specific	Declare and can participate in discussions on all topics as subject area is not being investigated by the guideline.
Nina Hallowell	Small share -holdings in AstraZeneca and GlaxoSmithKline	Personal Pecuniary Specific	Declare and can participate in discussions on all topics as share are part of a managed portfolio.

Maggie Alexander	Co-author of an article published in December 2011 on the way in which estimates of benefits from screening are calculated for Journal of Medical Screening.	Personal Non Pecuniary	Declare and can participate in discussions on all topics as screening is not being investigated by the guideline.
	Author of an article published in September 2012 on a continued commitment to better awareness, treatment and screening of breast cancer for the public service review	Personal Non Pecuniary	Declare and can participate in discussions on all topics as article was not specific to people with familial breast cancer.
	Interviewed for Sky News, discussing the facts and the current state of play for women considering preventative surgery.	Personal Non Pecuniary	Declare and can participate in all discussions as the interview was carried out after the last GDG meeting held on 2 November 2012 by which time all recommendations had been agreed.
Caitlin Palframan	Interviewed for Channel 5, discussing recent breast cancer research funded by Breakthrough Breast Cancer on the genetic code of hereditary breast cancer.	Personal Non Pecuniary	Declare and can participate in discussions on all topics as the genetic code of hereditary breast cancer is not being investigated by the guideline.
Anne Armstrong	No interests declared		
Kathie Binysh	No interests declared		
Andrew Cuthbert	No interests declared		
Diana Eccles	No interests declared		
Fiona Gilbert	No interests declared		
Ulrike Harrower	No interests declared		
Susan Heard	No interests declared		
Anneke Lucassen	No interests declared		
Ursula Van Mann	No interests declared		

Paul Pharoah	No interests declared		
Wendy Watson	No interests declared		
Amanda Taylor	No interests declared		

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Appendix D2

Members of the 2004 Guideline Development Group

GDG Chair

Professor Gareth Evans	Consultant in Clinical Geneticists St Mary's Hospital, Manchester

GDG Members

Nasim Bahar	Patient Representative
Dr Michelle Barclay	Patient Representative, Policy Manager, Breakthrough Breast Cancer
Professor Doug Easton	Professor of Genetic Epidemiology, University of Cambridge, Strangeways Research Laboratory
Dr Jon Emery	Cancer Research UK Clinician Scientist General Practice Research Unit, University of Cambridge
Dr Jonathan Grey	Consultant in Medical Genetics & Clinical Director Medical Genetics Service in Wales
Dr Jane Halpin	Public Health, Watford & Three Rivers PCT, St Albans
Dr Penny Hopwood	Consultant Psychiatrist and Psycho-Oncologist Christie Hospital NHS Trust Manchester
Aileen McIntosh	Deputy Director, Sheffield Evidence Based Guideline Programme, Public Health, ScHARR, University of Sheffield
Dr James Mackay	Consultant Genetic Oncologist, The Genetics Unit, Institute of Child Health, London
Carmal Sheppard	Consultant Nurse Breast Care, Portsmouth Hospital NHS Trust/University of Southampton
Mr Mark Sibbering Derby	Consultant Breast Surgeon, Derby City General Hospital,
Wendy Watson	Patient Representative, Herediatary Breast Cancer Helpline
Dr Allan Wailoo	Health Economist, Sheffield Health Economics Group ScHARR, University of Sheffield
Clare Shaw	Research Associate, Public Health, ScHARR University of Sheffield (until May 2003)
Professor Valarie Beral	Director, Department of Health Breast Screening Advisory Committee, also Cancer Research UK Epidemiology Unit University of Oxford, (until February 2003)

Co-Optees

Dr Sue Barter	Radiologist, Department of Diagnostic Radiology Bedford Hospital, Bedford
Sally Cottrell	Clinical Scientist, Medical Genetics Unit, St George's Hospital Medical School, London

In Attendance

Nancy Turnball	Chief Executive National Co-ordinating Centre for Primary Care
Karen Beck	Public Health ScHARR, University of Sheffield
Catherine Beverley	Information Officer ScHARR, University of Sheffield

Observers

Colette Marshall	National Institute for Clinical Excellence
Professor Neva Haites	Scottish Inter-collegiate Guideline Network (SIGN)

Appendix D3

Members of the 2006 Guideline Development Group

GDG Chair

Professor Gareth Evans	Consultant Clinical Geneticist, St Mary's Hospital, Manchester

GDG Members

Nasim Bahar	Patient Representative
Professor Doug Easton	Principle Research Fellow, Cancer Research UK
Dr Jane Halpin	Public Health, Watford & Three Rivers PCT, St. Albans
Dr Penny Hopwood	Consultant Psychiatrist and Psycho-Oncologist Christie Hospital NHS Trust, Manchester
Aileen McIntosh	Deputy Director, Sheffield Evidence Based Guidelines Programme Public Health, ScHARR, University of Sheffield
Carmel Sheppard	Consultant Nurse Breast Care, Portsmouth Hospitals NHS Trust/University of Southampton
Mr Mark Sibbering	Consultant Breast Surgeon, Derby City General Hospital, Derby
Wendy Watson	Patient representative,
Dr Sue Barter	Radiologist, Cambridge Breast Unit, Addenbrooke's Hospital Cambridge
Dr Cristina Parsons Perez	Senior Genetics, Policy and Information Officer, Breakthrough Breast Cancer
Dr Ken Young	Consultant Physicist, National Co-ordination Centre for the Physics of Mammography, Royal Surrey County Hospital NHS Trust, Guildford
Prof Fiona Gilbert	Radiologist, Foresterhill Aberdeen

Technical Team

Richard Norman	Health Economist
Gill Ritchie	Systematic Reviewer
Yolanda Jozephs	Project Manager
Nancy Turnbull	Chief Executive

Appendix D4

Organisations invited to comment on the guideline [2013]

The following stakeholders registered with NICE and were invited to comment on the scope and the draft version of this guideline

- Abbott Laboratories
- African HIV Policy Network
- Allocate Software PLC
- Amgen UK
- Association of Anaesthetists of Great Britain and Ireland
- Association of Breast Surgery
- Association of British Insurers
- Association of Cancer Physicians
- Association of Clinical Pathologists
- Association of Genetic Nurses and Counsellors
- Astrazeneca UK Ltd
- Birmingham Women's Health Care NHS Trust
- BME cancer communities
- Bradford District Care Trust
- Breakthrough Breast Cancer
- Breast Cancer Campaign
- Breast Cancer Care
- Breast Screening QA Reference Centre
- Breast Test Wales
- Bristol and Avon Chinese Women's Group
- British Association of Plastic Reconstructive and Aesthetic Surgeons
- British Association of Surgical Oncology
- British Dietetic Association
- British Medical Association
- British Medical Journal
- British National Formulary
- British Psychological Society
- BUPA Foundation
- C. R. Bard, Inc.
- Cambridge University Hospitals NHS Foundation Trust
- Camden Link
- Cancer Genetics Group
- Cancer Network User Partnership
- Cancer Research UK
- Cancer Services Co-ordinating Group
- Cancer Voices
- Capsulation PPS
- Care Quality Commission (CQC)
- Central South Coast Cancer Network

- CLIC Sargent
- Community District Nurses Association
- Covidien Ltd.
- Department for Communities and Local Government
- Department of Health
- Department of Health, Social Services and Public Safety - Northern Ireland
- Dorset Primary Care Trust
- Dudley Group Of Hospitals NHS Foundation Trust
- East and North Hertfordshire NHS Trust
- East Midlands Cancer Network
- Energy Therapy World-Wide Net
- Genetic Alliance UK
- George Eliot Hospital NHS Trust
- Gloucestershire Hospitals NHS Foundation Trust
- Gloucestershire LINk
- Great Western Hospitals NHS Foundation Trust
- Greater Midlands Cancer Network
- Hammersmith and Fulham Primary Care Trust
- Health Protection Agency
- Health Quality Improvement Partnership
- Healthcare Improvement Scotland
- Hindu Council UK
- Hull and East Yorkshire Hospitals NHS Trust
- Institute of Biomedical Science
- Integrity Care Services Ltd.
- International Early Pregnancy Research Group
- Johnson & Johnson Medical Ltd
- Joint Collegiate Council for Oncology
- KCARE
- Kent & Medway Cancer Network
- Lancashire Care NHS Foundation Trust
- Lancashire Teaching Hospitals NHS Trust
- London Cancer
- Luton and Dunstable Hospital NHS Trust
- Macmillan Cancer Support
- Medicines and Healthcare products Regulatory Agency
- Ministry of Defence
- National Cancer Action Team
- National Cancer Intelligence Network
- National Cancer Research Institute
- National Clinical Guideline Centre
- National Collaborating Centre for Mental Health
- National Collaborating Centre for Women's and Children's Health

- National Council for Palliative Care
- National Hereditary Breast Cancer Helpline
- National Institute for Health Research Health Technology Assessment Programme
- National Patient Safety Agency
- National Public Health Service for Wales
- National Radiotherapy Implementation Group
- National Treatment Agency for Substance Misuse
- NHS Clinical Knowledge Summaries
- NHS Connecting for Health
- NHS Direct
- NHS Hertfordshire
- NHS National Cancer Screening Programmes
- NHS Plus
- NHS Sussex
- NHS Warwickshire Primary Care Trust
- NICE - Centre for Evidence based Purchasing
- NICE – CPHE
- NICE - CPHE Methodology
- NICE - IMPLEMENTATION CONSULTANT Region – East
- NICE - IMPLEMENTATION CO-ORDINATION
- NICE - Medicines and Prescribing Centre
- NICE - NHS Evidence
- NICE – PPIP
- NICE - R&D for info
- NICE - Technical Appraisals
- North of England Cancer Network
- North Trent Cancer Network
- Northern Ireland Cancer Network
- Nova Healthcare
- Oxfordshire Primary Care Trust
- Peninsula Cancer Network
- Pfizer
- Public Health Agency
- Public Health Wales NHS Trust
- QResearch
- Rarer Cancers Foundation
- Roche Diagnostics
- Roche Products
- Royal Berkshire NHS Foundation Trust
- Royal College of General Practitioners
- Royal College of General Practitioners in Wales
- Royal College of Midwives
- Royal College of Nursing
- Royal College of Obstetricians and Gynaecologists

- Royal College of Paediatrics and Child Health
- Royal College of Paediatrics and Child Health, Gastroenetrology, Hepatology and Nutrition
- Royal College of Pathologists
- Royal College of Pathologists
- Royal College of Physicians
- Royal College of Psychiatrists
- Royal College of Radiologists
- Royal College of Surgeons of England
- Royal Free Hospital NHS Foundation Trust
- Royal Pharmaceutical Society
- Royal Society of Medicine
- Royal Surrey County Hospital NHS Trust
- Sandoz Ltd
- Sanofi
- Scottish Intercollegiate Guidelines Network
- Sheffield Teaching Hospitals NHS Foundation Trust
- Shropshire & Mid Wales Cancer Forum
- Social Care Institute for Excellence
- Society and College of Radiographers
- South Asian Health Foundation
- South Staffordshire Primary Care Trust
- South Wales Cancer Network
- South West Thames Regional Genetics Service
- South West Yorkshire Partnership NHS Foundation Trust
- St Mary's Hospital Solent Healthcare Nottingham City Hospital
- Step4Ward Adult Mental Health
- Sussex Cancer Network
- Target Ovarian Cancer
- The Association for Clinical Biochemistry
- The British In Vitro Diagnostics Association
- The Hindu Forum of Britain
- The National LGB&T Partnership
- The Rotherham NHS Foundation Trust
- The University of Glamorgan
- UCL Partners
- UK Clinical Pharmacy Association
- University Hospitals Coventry and Warwickshire NHS Trust
- University of Nottingham
- Walsall Local Involvement Network
- Welsh Government
- Welsh Scientific Advisory Committee
- West Midlands Ambulance Service NHS Trust

- Western Cheshire Primary Care Trust
- Westminster Local Involvement Network
- Wirral University Teaching Hospital NHS Foundation Trust
- York Hospitals NHS Foundation Trust
- Yorkshire Ambulance Service NHS Trust
- Yorkshire Cancer Network

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Appendix D5

Individuals carrying out literature reviews and complementary work [2013]

Dr John Graham	Director, National Collaborating Centre for Cancer, Cardiff

Overall Co-ordinators

Dr Andrew Champion	Centre Manager, National Collaborating Centre for Cancer, Cardiff
Angela Bennett	Assistant Centre Manager, National Collaborating Centre for Cancer, Cardiff

Project Manager

Lianne Gwillim	National Collaborating Centre for Cancer, Cardiff

Researchers

Dr Nathan Bromham	Senior Researcher, National Collaborating Centre for Cancer, Cardiff
Dr Susan O'Connell	National Collaborating Centre for Cancer, Cardiff
Dr Jennifer Hilgart	National Collaborating Centre for Cancer, Cardiff
Dr Catrin Lewis	National Collaborating Centre for Cancer, Cardiff

Information Specialists

Sabine Berendse	National Collaborating Centre for Cancer, Cardiff
Stephanie Arnold	National Collaborating Centre for Cancer, Cardiff

Health Economists

Professor Ceri Phillips	Professor of Health Economics, Swansea Centre for Health Economics, Swansea University
Dr Deborah Fitzsimmons	Reader, Swansea Centre for Health Economics, Swansea University
Dr Bernadette Sewell	Health Economics Researcher, Swansea Centre for Health Economics, Swansea University
Hayley Bennett	Health Economic Modeller, Swansea Centre for Health Economics, Swansea University

Needs Assessment

Dr Joyce S Solomons	Consultant of Clinical Genetics, University Hospitals of Leicester NHS Trust

Appendix D6

Members of the NICE project team [2013]

Sarah Willett
Associate Director, Centre for Clinical Practice

Claire Turner
Guideline Commissioning Manager

Anthony Gildea[36]
Guideline Coordinator

Carl Dawood[37]
Guideline Coordinator

Nichole Taske
Technical Lead

Jasdeep Hayre
Technical Analyst (Health Economics)

Anne-Louise Clayton
Medical Editor

Barbara Meredith
Patient Involvement Lead

[36] Until August 2012
[37] From September 2012