Protocol 1
Management guidelines for unaffected women with a family history of breast and/or ovarian cancer
Frequently asked questions

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If you have any additional questions or comments please email cancergenetics@rmh.nhs.uk

Q: What are the risk categories for mammographic surveillance?
There are three categories for mammographic surveillance
A -Population risk (mammographic surveillance according to NHSBSP only)
B -Increased risk (additional mammographic surveillance above NHSBSP-see below)
C -High risk (BRCA1, BRCA2 and TP53 carriers) – see Protocol 3 and Protocol 4.

Q: What mammographic surveillance is offered to women in category B?
Women are either offered annual mammography between 40-50 years and three-yearly mammography within the NHSBSP thereafter (B1 category) or annual mammography 40-60 years and three-yearly mammography within the NHSBSP thereafter (B2 category) dependant on their level of risk.

Q: How do the risk categories compare to those used in the NICE recommendations?
The minimal family history required for category B1 surveillance is equivalent to the NICE moderate risk category. Women in the NICE high risk category are assigned either B1 or B2 surveillance dependent on their estimated risk of breast cancer. The guidelines for mammography in women with a family history of breast cancer that were published in 2013 by NICE are available at: http://guidance.nice.org.uk/CG164 .

Q: What is NHSBSP?
NHSBSP stands for the National Health Service Breast Screening Programme (http://www.cancerscreening.nhs.uk/breastscreen/). This service provides breast surveillance every three years for all women in the UK aged 47-73 years. Women receive an invitation to attend mammography, via a rolling schedule, thus all women will receive their first mammogram between ages 47-50 years. Women above the age of 73 can continue to receive three-yearly mammograms via self-referral to their local breast screening unit.

Q: Is any mammographic surveillance offered below 40 years?
No mammography is recommended to women below 40 years. This is because the absolute risk of developing breast cancer at this age in women who are not proven gene carriers is low. Women at high risk, due to a gene mutation are offered MRI (see Protocols 3 and 4)
Furthermore, the sensitivity of mammography is reduced in this age group. Women should be advised to perform breast self-awareness.
(See http://www.cancerscreening.nhs.uk/breastscreen/breastawareness.html

Q: What do FDR, SDR and TDR stand for?
FDR = first-degree relative e.g. sister, mother, daughter.
SDR = second-degree relative e.g. grandmother, aunt.
TDR = third-degree relative e.g. cousin, great-aunt, great-grandmother.

Q: Should the consultee always have a first-degree relative with breast / ovarian cancer?
If the consultee only has one or two relatives affected with breast and/or ovarian cancer, a first-degree relative must be affected. If three or more relatives are affected, a FDR is not

required for B1 surveillance, but is required for B2 surveillance. See Protocol 1 for specific details. See below regarding pedigrees with intervening male relatives.

Q: How should intervening male relatives be considered when assessing family history?
A *single* shift up in relatedness is allowed if there is an intervening male relative. For example an affected paternal aunt should be considered as a first-degree relative instead of a second-degree relative. An affected cousin through a maternal uncle or a paternal uncle should be counted as a second-degree rather than a third-degree relative.

Q: How should intervening unaffected female relatives be considered when assessing family history?
When assessing family history for mammographic surveillance, unaffected female relatives do not change the position of other family members within the pedigree.

Q: How should half-siblings be considered when assessing a family history for mammographic surveillance recommendations?
Half-siblings through a female are classed as second-degree relatives, for mammographic surveillance assessment. Half-siblings through a male are classed as first-degree relatives.

Q: What if the age of breast cancers in some relatives is unknown?
An estimated decade of age of the cancer occurring should be used if possible. Otherwise assume the breast cancer occurred at age 60 years.

Q: What should I do if there is limited family history available?
Only the available history should be taken into account.

Q: Should *in situ* breast cancer be included in the assessment?
Yes. In situ cancer, such as DCIS (ductal carcinoma in situ) and LCIS (lobular carcinoma in situ), should be included in the same way as invasive breast cancer in assessment for mammographic surveillance.

Q: How should multiple metachronous ipsilateral breast cancers be assessed?
Two (or more) separate, ipsilateral breast cancers which have occurred 5 or more years apart should be managed as separate cancers for mammographic surveillance stratification (i.e. they should be counted as a bilateral breast cancer), unless it is clear that the cancer is a recurrence. This is a pragmatic approach as it is usually not possible to robustly identify which are separate primaries and which recurrence, but most are likely to be separate cancers.

Q: How should multiple synchronous ipsilateral breast cancers be assessed?
These should be counted as a single breast cancer for mammographic surveillance stratification. Simultaneous ipsilateral breast cancers are sometimes termed multifocal or multicentric.

Q: How should bilateral breast cancer be assessed?
The protocol criteria relate to the number of relatives affected with cancer including those with bilateral breast cancer, rather than the total number of cancers.

Q: What mammographic surveillance should be offered to the consultee if she is affected with breast cancer herself?
Standard clinical care of women with early or locally advanced breast cancer (defined as breast cancer which is present in breast tissue and lymph nodes only) is to have annual mammography until they enter NHSBSP. If women are already eligible for NHSBSP when

they are diagnosed, they additionally have annual mammography for 5 years (NICE Guideline 80: http://guidance.nice.org.uk/CG80).

A consultee who is herself affected with breast cancer should be managed in the same way as a FDR when assessing family history. Affected women who are in the B1 category are unlikely to require any surveillance additional to that instituted as part of their breast cancer management, as they have annual mammography until entering NHSBSP. Affected women who are in the B2 category may require annual mammography between 50-60 years, if they were diagnosed <50 years.

Q: Can relatives in a family receive different levels of mammographic surveillance?
The level of mammographic surveillance a person receives is based on an individual's position within a pedigree. Therefore, in some families different relatives will be eligible for different levels of surveillance. For example, the daughters of two sisters who have a common affected maternal grandmother would receive different surveillance if only one of the sisters is affected with breast cancer.

Q: When should I consider BRCA mutation testing?
A BRCA test should be undertaken if a member of the family meets the eligibility criteria outlined in Protocol 2.

Q: What breast surveillance should I recommend in families with a negative BRCA test?
The surveillance should be recommended according to Protocol 1.

- In breast-ovarian cancer families, a negative BRCA test may alter the surveillance recommendation and the breast surveillance category should be calculated on the basis of the breast cancers alone.
- In breast cancer only families a negative BRCA test does not alter the surveillance recommendation.
- Individuals with breast cancer and residual breast tissue should be recommended the appropriate breast surveillance, if they are no longer in follow-up for their cancer.

Q: Should MRI be recommended in BRCA negative families?
No. If an untested individual from a BRCA negative family meets the NICE recommended threshold for MRI, they will also meet the criteria for BRCA unaffected testing (see below). Thus a BRCA test should be performed in the individual and MRI only instituted if a mutation is identified.

Q: When should I discuss risk-reducing bilateral mastectomy?
Risk-reducing bilateral mastectomy should be discussed in BRCA1, BRCA2 and TP53 mutation carriers – see Protocol 3 and Protocol 4.

The lifetime risk of BRCA negative families will only very exceptionally reach those seen in BRCA carriers.
BRCA negative families with the following structure should be discussed / evaluated to see if discussion of risk-reducing bilateral mastectomy is warranted for unaffected first-degree relatives of breast cancer cases:

- Five or more cases of breast cancer <60 years *or*
- Four cases of breast cancer <50yrs (all at least TDR)

For BRCA negative families with four or fewer breast cancer cases risk-reducing bilateral mastectomy should not be discussed unless raised by the individual. Women from such

families may still wish to consider mastectomy due to personal reasons, but the risks in these families do not warrant recommendation based on genetic risk. All cases should be discussed in the MDT.

Q: When should I discuss ovarian risk?
Ovarian risk should be discussed:

- In women with BRCA1 or BRCA2 mutations – see Protocol 3.
- In BRCA negative families, if the consultee has two or more first or second-degree relatives with ovarian cancer. At least one should be a first-degree relative of the consultee. At least two of the ovarian cancer cases should be first-degree relatives of each other. Risk-reducing bilateral salpingo-oophorectomy can be considered after child-bearing is complete and can be offered from 50 years, or earlier if two or more ovarian cancers occurred before 50 years.
- Ovarian surveillance should not be recommended outside of a research study.

In BRCA negative families with breast cancer only, no discussion, surveillance or risk-reducing surgery for ovarian cancer is required. There is no evidence of a significant increase in ovarian cancer risk in such families.

Q: When should I discuss chemoprevention?
Chemoprevention can be discussed and offered to any women in B2 category or BRCA2 carriers (see protocol 3). Chemoprevention should not be offered to BRCA1 carriers. NICE guidance 164 recommends that chemoprevention can be considered in women at moderate risk (i.e B1 category), but we are not recommending offering it to this group at present until further data is collected on the risks and benefits for this risk group.

Q: What benefits of chemoprevention should I discuss?
Women should be made aware that chemoprevention reduces the overall number of ER positive breast cancer cases that develop, but does not have any impact on mortality.

Q: What major side effects of chemoprevention should I discuss?
Tamoxifen use is associated with a small increased risk of endometrial cancer and venous thromboembolism.

Q: What minor side effects of chemoprevention should I discuss?
Common side effects include menopausal symptoms such as hot flushes and vaginal discharge or dryness. Some patients can experience mild nausea, weight gain and muscle and joint pains. Many women find that the side effects of chemoprevention are significant enough to stop taking the medication. Studies report that about 1 in 5 women will stop taking chemoprevention due to side effects.

Q: Are there any contraindications to chemoprevention?

- Tamoxifen should not be taken if there is a personal or family history of blood clots or a family history of endometrial cancer.
- Tamoxifen and raloxifene should not be taken with HRT (Hormone Replacement Therapy) or the contraceptive pill.
- Tamoxifen or raloxifene can also interfere with the action of other drugs, so it is important for the prescribing Doctor to take a drug history
- Tamoxifen and raloxifene should not be taken if woman is trying to conceive.

Q: At what age can chemoprevention be started?
Chemoprevention should not be started prior to age 35.

Q: How long can chemoprevention be taken?
A maximum of 5 years is recommended.

Q: Who will prescribe chemoprevention?
Following discussion in a Specialist Genetics or Family history clinic, a letter can be sent to the patients GP to prescribe chemoprevention, should the patient wish to pursue this.