Background

This document gives guidance on risk assessment for patients with a family history (FH) of breast cancer seen in Secondary Care FH clinics and referral pathways to the Regional Genetics Services in Leeds/Sheffield. This is based on the NICE Familial Breast Cancer Guidelines (CG164 June 2013), and regionally-agreed Commissioning. Separate information is available for risk assessment in Primary Care (GP) and referral pathways to Secondary Care.
Pathway for Secondary Care Assessment (Breast FH Clinics)
+/- Referral To Tertiary Care if indicated

Patient attends after referral – criteria for acceptance met

Take and record family history (refer to Clinical Genetics if there is a known BRCA1/BRCA2 or other predisposing gene mutation identified in the family)

Near-Population Risk? e.g. (with no Jewish FH, or TNT cases <40, or bilateral, or other relevant cancers):
- 1 female FDR Ca breast only >=40 years
- 1 female FDR Ca breast only on paternal side
- FH on maternal side, but mother unaffected (mother or other relatives may seek advice)
- 2 female FDR/SDR Ca breast >= 40, but unrelated to each other

Yes
No further assessment -> Refer back to Primary Care

No

Clear Moderate Risk? e.g. (with no Jewish FH, or TNT cases <40, or bilateral, or other relevant cancers):
- 1 female FDR Ca breast only <40 years
- 1 male FDR Ca breast only
- 2 female FDR or 1 FDR + 1 SDR (related to each other) Ca breast >=40

Yes
No further risk assessment. Manage in Secondary Care as for Moderate risk

No

Calculate lifetime risk of breast cancer using IBIS/Tyrer-Cuzick programme
Calculate Manchester Score if ovarian or pancreatic or prostate cancer in family

Are any of these criteria met?:
- Known BRCA1/BRCA2 or other predisposing gene mutation in family
- Lifetime risk of breast cancer >=30%
- BRCA1/2 carrier probability from IBIS/Tyrer-Cuzick >=10%
- Family Manchester Score >=15
- Affected with TNT breast cancer <40
- Ashkenazi Jewish FH
- NICE CG164 risk grouping for referral to Genetics

(Seek advice from Clinical Genetics for unusual FHs)

No
Manage in Secondary Care according to risk level indicated by IBIS/Tyrer-Cuzick.

Yes
Refer to Clinical Genetics for further assessment and advice
**Family History Taking**

A family pedigree should be taken and recorded. This should include information at least as far as grandparents and first cousins on both maternal and paternal sides of the family. Ages of unaffected relatives alive or deceased, types of cancer in affected relatives and ages affected should be recorded.

Ask if there is Ashkenazi Jewish heritage, or any known breast/ovary cancer mutation in the family.

If type of cancer is not known, type should not be inferred, unless there is supporting evidence (e.g. type of surgery). Bear in mind that some cancers are commonly misreported, e.g. carcinoma/CIS of cervix in younger women reported as ovarian cancer. Ask supplementary questions e.g. type of treatment received.

If age of cancer is unknown, estimate as age of death (if known) or 60 years (if age of death not known).

Confirmations of cancer diagnoses are not routinely recommended in Secondary Care risk assessment, unless the patient/family are able to provide information e.g. death certificates. It may be appropriate in some cases to defer risk assessment until after the referred patient has consulted relatives. Secondary Care risk assessment should be based on best available information. In cases meeting criteria for referral to tertiary care, Genetics may seek confirmations e.g. Cancer Registry data.

**Use of Tyrer-Cuzick (IBIS) Risk Evaluator Programme**

This runs as an executable file on Windows. The latest version of the programme should be used (at the time of writing v7.02). This is available from: [http://www.ems-trials.org/riskevaluator/](http://www.ems-trials.org/riskevaluator/)
See above pathway. For patients clearly falling into near-population or moderate risk, use of the Tyrer-Cuzick (T-C) programme is not required nor recommended. For more complicated FHs, the programme should be used, inputting the information obtained from the family history taking.

For the purposes of determining eligibility for referral to Genetics, only cancer FH/ages should be inputted; data on parity, benign breast disease, height/weight, menopausal status, HRT use should not be inputted. Patients where the lifetime risk is >=30%, or the BRCA1+BRCA2 probability is >=10% will be eligible for referral to Genetics.

Additional notes:

- Lifetime risk is from age 20 years. If the patient is significantly older, lifetime risk may be estimated by inputting the patient's age as 20 years. The risk from 20-40 years will usually be <3% unless there is a very high risk FH, so for most women <40 years making this change will not adjust the risk grouping

- Patients with a lifetime risk of >=17% and <30% fall into the moderate risk group category

- For patients close to 40 years, breast cancer risk from 40-49 years may also be calculated (input patient's age as 40) – eligible for referral to Genetics if >8%; moderate risk if 3-8%

- T-C allows the consultand to be inputted as affected with ovarian cancer, but not with breast cancer. If the patient has been affected with breast cancer themselves, T-C may still be used to estimate the family risk by considering the risk to an unaffected female FDR. The Manchester Score (see below) may additionally be used to determine eligibility for referral of affected patients to Genetics

- DCIS counted as breast cancer, but LCIS and other pre-invasive conditions not counted

- T-C allows a brother and/or father to be inputted as affected with breast cancer, and allows Ashkenazi inheritance to be included in the risk assessment

- Not all relevant FHs can be inputted into T-C e.g. affected relatives beyond grandparents, prostate/pancreas cancer affected cases. Using the Manchester Score (see below) +/- seeking advice from Genetics is advised where the FH is complicated and there remains concern that the patient may be at high risk

**Manchester Scoring System**

The Manchester Scoring System (MSS) may be used to assess the likelihood of a BRCA1/2 mutation being present in a family. It does not specifically indicate breast cancer risk.

Use of MSS is particularly recommended: where the FH includes ovary/pancreas/prostate cancer; for FHs where not all affected relatives can be included in the T-C programme; where the referred patient is affected with breast/ovarian cancer

The Combined (BRCA1+BRCA2) Score is calculated by adding up the scores for each cancer in a direct blood lineage (all individual cancers in a total score cancers must be on the same side of the family).
Patients may be referred to Genetics for further advice where there is a family Manchester Score of $\geq 15$. Affected patients from such families are likely to be eligible for genetic testing in the first instance, with predictive testing available to unaffected relatives if a mutation is found. Where there is no available affected family member for initial screening, FDRs of an affected family member may be offered testing where there is a Score of $\geq 17$.

Scores are as follows:

- FBC <30 – Score 11
- FBC 30-39 – Score 8
- FBC 40-49 – Score 6
- FBC 50-59 – Score 4
- FBC >59 – Score 2
- MBC <60 – Score 13
- MBC >59 – Score 10
- Ovarian Ca <60 – Score 13
- Ovarian Ca >59 – Score 10
- Pancreatic Ca – Score 1
- Prostate Ca <60 – Score 2
- Prostate Ca >59 – Score 1

Additional notes:

- FBC = female breast cancer; MBC = Male breast cancer.

- One intervening unaffected female is allowed. A further intervening female relative is allowed if they have had risk-reducing mastectomy or oophorectomy before the age of natural menopause (<50 years). Cancers through any additional female intervening individuals are not included.

- Cancers through unaffected intervening males are counted.

- Ovarian cancers of mucinous, borderline and germ cell (except granulosa cell) histological types score 0 points, if the histology is known. These are the minority types, and therefore if the histology is not known, count score 10/13 as above.

- If the exact age of the cancer at diagnosis is unknown, a best estimate should be used if possible. If there is no information, the cancer will be assumed to have been diagnosed at 60 years.

- Modification of the Combined Score (by +/- 1 to 4 points maximum) is made based on breast cancer pathological information, if available. Modification may be made for the index case (or closest relative for unaffected cases under consideration for genetic testing): HER2 +ve – Score -4; Lobular breast cancer – Score -2; DCIS only (no invasive cancer) – Score -1; LCIS only – Score -4*; Grade 1 – Score -2; Grade 3 – Score +2; ER +ve – Score -1; ER -ve – Score +1; Grade 3 Triple negative – Score +4.
Rare Conditions

Rare conditions predisposing to breast cancer should be considered and if particular features are present, seek advice from Genetics.

These include:

- **Cowden Syndrome.** Large head size, facial/oral papules, endometrial cancer, thyroid (especially follicular) cancer, renal cell cancer, breast cancer
- **Peutz-Jeghers Syndrome.** Mucocutaneous (especially lips/buccal) pigmentation, intussusception, hamartomatous bowel polyps, gastrointestinal and breast cancers
- **Li Fraumeni Syndrome.** Young breast cancer cases with other cancers <45 years especially sarcomas, gliomas, choroid plexus carcinoma, adrenal cell cancer, leukaemia
- **Hereditary diffuse gastric cancer.** Lobular breast cancer and diffuse-type stomach cancer (especially <40 years)

For Patients Referred to Genetics

Inform the patient that referral does not mean that they will be automatically be assessed as high risk or offered genetic testing.

A further risk assessment will be performed, which may include a FH questionnaire, confirmation of relevant family cancer diagnoses, and use of another risk assessment method (e.g. BOADICEA).

If genetic testing is performed in the family, the risk will be reassessed dependent on the results.

Risk Levels and Breast Screening Available

**Moderate risk unaffected:** 40-49 years annual mammography; 50-59 years 18-monthly mammography (alternating with NHSBSP); then NHSBSP 3-yearly

**High risk unaffected (<=30% BRCA carrier probability):** 40-49 years annual mammography; 50-59 annual mammography (may include NHSBSP screen); then NHSBSP 3-yearly

**High risk unaffected (untested, >30% BRCA carrier probability):** Refer to NHSBSP high risk screening programme – 30-49 years annual MRI (+ mammography from 40 years); 50-59 years annual MRI and mammography if dense breast pattern, otherwise annual mammography alone; then NHSBSP 3-yearly.

**High risk unaffected (BRCA1 or BRCA2 carrier; not had prophylactic mastectomies):** Refer to NHSBSP high risk screening programme – 30-49 years annual MRI (+ mammography from 40 years); 50-59 years annual MRI and mammography if dense breast pattern, otherwise annual mammography alone; 60-69 years annual mammography, then NHSBSP 3-yearly.
As per NICE guidelines for affected women. As per NICE guidelines for TP53 families. As for NICE/specialist guidelines for other rare conditions.

Note that as thresholds fall, and more testing is performed, genetic testing will increasingly determine eligibility or otherwise for high risk screening.

**Risk Levels and Tamoxifen**

**Moderate/High risk unaffected women:**

Ask about possible contraindications especially personal or close family history of thromboembolism, or personal history of endometrial cancer. Ask about drug history for possible adverse interactions especially rifampicin, warfarin/other coumarin anticoagulants, fluoxetine/paroxetine antidepressants, antipsychotics, bupropion, cinacalet. Discuss with medical staff and GP if uncertain if there is a contraindication or adverse interaction. Discuss appropriate contraception for pre-menopausal women.

Offer Tamoxifen over 35 years of age. Use T-C risk assessment if required to guide patients as to risk/benefit over different age ranges over 35 years. Discuss and provide information on benefits, risks and contraindications. Ask GP to prescribe if appropriate.