Scottish familial breast cancer

> This consensus document is not a rigid constraint on clinical practice, but a concept of good practice against which the needs of the individual patient should be considered. It therefore remains the responsibility of the individual clinician to interpret the application of these guidelines, taking into account local service constraints and the needs and wishes of the patient. It is not intended that these consensus documents are applied as rigid clinical protocols.

This consensus document forms the framework for undertaking germline genetic testing and risk assessment for breast cancer predisposition in Scotland. This update of guidance is in response to updates to NICE guidance.

Close all

Genetic testing: breast and ovarian cancer predisposition

The offer of a gene panel test should be considered for individuals diagnosed with a cancer that meet one or more of the following criteria.

Eligibility Criteria:

Patient diagnosed with

- Breast cancer under age 40
- Bilateral breast cancer, both under age 60
- Triple negative breast cancer (TNBC), under 60
- Breast cancer under 45 with (at least) one 1st degree relative under age 45
- Breast cancer AND ovarian cancer, any age
- Male breast cancer, any age
- Epithelial ovarian cancer, any age
- Breast cancer AND 10% or more probability of mutation based on CanRisk(https://www.canrisk.org/) (all genes) or a Manchester score(/national-cancer-management-pathways-under-development/breast-cancer/scottish-familial-breast-cancer/manchester-scoring-system/) of 15 or more.

Genes to be tested

Personal or relevant family history of breast cancer: Breast panel: BRCA1, BRCA2, TP53, PALB2, PTEN, STK11, ATM, CHEK2, RAD51C and RAD51D. CDH1 is not included in the panel however can be added when appropriate eligibility criteria* met.

Personal or relevant family history of ovarian cancer: Ovarian Panel: BRCA1, BRCA2, MLH1, MSH2, MSH6, RAD51C, RAD51D, PALB2 and BRIP1

*CDH1 criteria for testing:

- Lobular breast cancer and diffuse gastric cancer (both <70 years).
- Bilateral or multiple ipsilateral lobular breast cancer <50 years
- Lobular breast cancer <70 years plus≥1 FDR/SDR with diffuse gastric cancer at any age
- Lobular breast cancer and ≥FDR/SDR has diffuse gastric cancer (≥ 1 case occurred < 70 years).

Types of Testing

- **Treatment Focused Testing:** Testing in patients to inform treatment or follow up may be undertaken by a Registered Healthcare professional involved in the patient's care, following local protocols. Testing is generally restricted to breast surgery and oncology teams. If eligibility is uncertain, the patient can be referred to the Genetic Services for assessment of eligibility or additional discussion.

- **Testing for a person with no personal history of breast cancer but with an available affected relative who meets the criteria for testing:** The person with no personal history of cancer should be advised to ask their relative to seek testing (via their own cancer service or via their local genetic services). If it is not possible to test a living affected relative, it may be possible for testing to be carried out in a deceased relative affected with breast or ovarian cancer, if there is
    - A tissue sample available for DNA extraction, AND
    - Pathology-adjusted Manchester score ≥17 or CanRisk score(https://www.canrisk.org/) ≥15%, AND
    - No living affected individual is available for genetic testing

- **Testing for a person with a family history, but no personal, history of breast / ovarian cancer and no available affected relative to test (unaffected testing):** Genetic testing can be offered by clinical genetics to an unaffected individual if their Manchester score is ≥19 , or their mutation probability on CanRisk is ≥10%.

- **Testing for a person with a known pathogenic mutation in the family:** If a pathogenic or likely pathogenic variant is identified in an individual, then relatives also at risk of inheriting the variant can be offered testing regardless of whether they have had cancer or not. The Clinical Genetics team cascades and undertakes the offer of predictive testing to at-risk relatives.

()Assessing Risk following Genetic Testing

The following outcomes of testing will confer a very high risk (>40% lifetime risk) of breast cancer in female

- Heterozygous pathogenic or likely pathogenic variants in BRCA1, BRCA2, TP53, PALB2, STK11, PTEN and CDH1.
- Heterozygous c.7271T>G variant in ATM
- Homozygous or compound heterozygous pathogenic or likely pathogenic mutations in ATM and CHEK2.

Heterozygous pathogenic or likely pathogenic variants in ATM, CHEK2, RAD51C and RAD51D are generally considered to confer a moderately increased risk (lifetime risk between 17-30%). However, an individualised risk assessment using CanRisk should be completed to factor in both genetic test results and family history.

Radiation Contraindications

Radiation is contraindicated in individuals with ATM homozygote (or compound hetrozygote) or *TP53* heterozygote pathogenic or likely pathogenic variants.

Enhanced screening for females** with an increased risk of breast cancer

**Female being used to refer to those assigned female at birth and who have not had any masculising or gender affirming treatments. Any patients who have had such treatment would need personalised risk assessment.

Family History

Females being considered for enhanced screening based on family history should be referred to a family history clinic for assessment of risk and need for family-based hereditary cancer gene panel testing.

Confirmation of Family History

For accurate risk estimation, the following are required:

- age of diagnosis of affected relatives and cancer site and type.
- current age or age of death of unaffected close relatives.

Confirmation of relatives' cancer diagnosis using medical records, cancer registry or death certificates should be performed for abdominal malignancies wherever possible. In general, it is not necessary to validate breast cancer-only histories. However, when substantial

management decisions, i.e. risk-reducing surgery, are being considered and no mutation has been identified, breast cancer history should be verified. Where no family history verification is possible, agreement by a multidisciplinary team should be sought before proceeding with risk-reducing surgery.

Females affected with breast cancer and a family history

Following discharge from cancer services, females affected with breast cancer, who are either not eligible for genetic testing or who have not been found to carry a pathogenic/likely pathogenic variant on testing, should receive surveillance equivalent to those with the same family history but without a personal history of breast cancer.

Definition of risk categories

Very high risk: gene carrier

Risk figures	Category description
• Equates to a lifetime risk of developing breast cancer of 40% or more, • Equates to a female in her thirties whose 10-year risk is greater than 8% as assessed at age 30, • or in her forties and whose 10-year risk is greater than 12% as assessed at age 40.	• Heterozygous carrier of a mutat *BRCA2, TP53, PALB2, STK11, PTEI* • Heterozygous carrier of c.7271T> • Homozygous mutations in *ATM,*

High risk

Risk figures	Category description
• Equates to a lifetime risk of developing breast cancer of 30% or more, • Equates to a female in her thirties whose 10-year risk is greater than 8% but less than 12% as assessed at age 40.	• Families where there is an estim greater risk of carrying a mutati risk gene • Heterozygous carries of a mutat RAD51D, ATM or CHEK2 and a C estimate of over 30% lifetime risk The individual being assessed should degree relative of an affected family r

	second-degree relative through an ur male. Affected individuals should be first-de of each other or related through unaf

Moderate risk

Risk figures	Category description
• Equates to a lifetime risk of breast cancer of greater than 17% but less than 30%, • Equates to a female in her thirties whose 10-year risk is greater than 3% but less than 8% as assessed at age 40.	• *A case of bilateral breast cancer treated as the equivalent of 2 af relatives.* • One first-degree* relative with b diagnosed under the age of 40, degree relative with male breast diagnosed at any age, • or two first- or one first- and one degree relative with breast canc ovarian cancer at any age, on th of the family, • or three first- or second-degree breast or ovarian cancer on the the family where one is a first-de of the individual under review or father • Heterozygous carrier of a mutat RAD51D, ATM or CHEK2 and a C estimate of 17-30% lifetime risk • Females with a diagnosis of Neu A case of bilateral breast cancer shou as the equivalent of 2 affected relative

Low risk

Risk figures	Category description
• Equates to 17% or less lifetime risk	• Anyone not fulfilling moderate, h high risk criteria

*A first-degree female relative is mother, father, daughter, son, sister or brother. A second-degree female relative is grandmother, grandfather, granddaughter, grandson, aunt, uncle, niece, nephew, half-sister or half-brother.

Breast screening protocols by risk category

Very high risk

- Heterozygous carrier of a mutation in *BRCA1, BRCA2, PALB2, STK11, PTEN and CDH1.*
- Heterozygous carrier of c.7271T>G *ATM*
- Homozygous mutations in *ATM, CHEK2*
- Female with a lifetime risk of developing breast cancer of 40% or more (see category definitions)

Age (years)	Test	Frequency
25-29*	MRI	Annual
30-39	MRI	Annual
40-50	MRI + mammography	Annual
51-70	Mammography (+/-MRI)**	Annual

*To qualify for screening under 30 years female must be a BRCA1, BRCA2 or PALB2 carrier AND have an 8% or greater 10 year risk at the age when entered.

**Continue with MRI screening only if significant breast density persists.

Very high risk: TP53 Carriers

Age (years)	Test	Frequency
20-70	MRI	Annual

Very high risk: A-T homozygotes

Age (years)	Test	Frequency
25-70	MRI	Annual

Untested females with 50% or greater risk of a mutation in a high-risk gene

- Very High Risk protocol up to age 50 when this should be reviewed.
- If the female remains untested after age 50 years, they move to the High Risk protocol.

High risk

- Equates to a lifetime risk of developing breast cancer of 30% or more, or greater than 8% 10-year risk between 40 and 50 years of age

Age (years)	Test	Frequency
35-39*	Mammography	Biennial
40-49	Mammography	Annual
50-59	Mammography	Annual
60-70	Mammography	18 monthly

*Screening starts at 35 years or 5 years earlier than the youngest age of onset in the family (but not before 30 years)

Moderate risk

- Equates to a lifetime risk of breast cancer of greater than 17% but less than 30% **or**
- a 10-year risk between 40 and 50 years of age which is greater than 3% but less than 8%

Age (years)	Test	Frequency
35-39*	Mammography	Biennial
40-49	Mammography	Annual
50-70	Mammography	3 yearly (NBSP)

*Screening starts at 40 years or 5 years earlier than the youngest age of onset in the family (but not before 35 years)

Low risk

Age (years)	Test	Frequency
50-70	Mammography	3 yearly (NBSP)

Printable version of Risk Category and Screening Protocols Summary(/media/2200/famillial-breast-cancer-summary-of-risk-and-screening.pdf)

Recommendations for all females having surveillance

- All screening mammography should be digital and performed at centres providing mammography to national breast screening programme standards.
- Ensure that individual strategies are developed for all female 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.
- Ensure that MRI surveillance includes MRI of both breasts performed to national breast screening programme standards.
- Ensure a robust recall system is in place equivalent to national breast screening programme.

Chemoprevention

Healthcare professionals should discuss the absolute benefits and risks of options for chemoprevention with females at **HIGH risk** and **MODERATE risk** of breast cancer.

NICE guidance as summarised below should be followed:

Females with no personal history of breast cancer at HIGH RISK

- Offer tamoxifen for 5 years to premenopausal females at high risk unless they have a past history or may be at increased risk of thromboembolic disease or endometrial cancer.
- Offer anastrozole for 5 years to post menopausal females at high risk unless they have severe osteoporosis (off-label use).

- Females with or at risk of osteoporosis should have their bone mineral density assessed when starting treatment and then at regular intervals. Treatment or prophylaxis for osteoporosis should be started when needed and carefully monitored.

For post menopausal females at high risk who have severe osteoporosis or do not wish to take anastrozole:

- Offer tamoxifen if they have no history thromboembolic disease or endometrial cancer

or

- Consider raloxifene (off-label use) for 5 years for females with a uterus if they have no history thromboembolic disease or endometrial cancer and do not wish to take tamoxifen

Chemoprevention is NOT RECOMMENDED in those with pathogenic or likely pathogenic variants in *BRCA1.*

F**emales with no personal history of breast cancer at MODERATE RISK**

- Consider tamoxifen for 5 years to premenopausal females unless they have a past history or may be at increased risk of thromboembolic disease or endometrial cancer.
- Consider anastrozole for 5 years to post menopausal female unless they have severe osteoporosis (off-label use).

For postmenopausal female at moderate risk who have severe osteoporosis or do not wish to take anastrozole:

- Consider tamoxifen if they have no history thromboembolic disease or endometrial cancer

or

- Consider raloxifene (off-label use) for 5 years for females with a uterus if they have no history thromboembolic disease or endometrial cancer and do not wish to take tamoxifen

Anastrozole, tamoxifien or raloxifen should not be taken for more than 5 years. Tamoxifen should be discontinued at least 2 months before trying to conceive a pregnancy and 6 weeks before planned surgery.

Patient Information Leaflets(https://www.ukcgg.org/information-education/ukcgg-leaflets-and-guidelines/) have been produced by the UK Cancer Genetic Group.

Risk reducing mastectomy

Females affected with breast cancer

Discuss the risks and benefits of risk-reducing mastectomy with females with a known pathogenic or likely pathogenic mutation conferring a very high risk of breast cancer, or those assessed to be at >30% lifetime risk of breast cancer.

Females with no personal history of breast cancer

Bilateral risk-reducing mastectomy is appropriate only for a small proportion of females who are at high or very high risk (>30% lifetime risk) and should be managed by a multidisciplinary team.

- Family history should be verified where no mutation has been identified before bilateral risk-reducing mastectomy. Where no family history verification is possible, agreement by a multidisciplinary team should be sought before proceeding with bilateral risk- reducing mastectomy.

Risk reducing bilateral salpingo-oophorectomy

- Discuss the risks and benefits of risk-reducing bilateral salpingo-oophorectomy with females with a known pathogenic or likely pathogenic mutation in a gene known to increase the risk of ovarian cancer or a family history assessed to increase the risk of ovarian cancer by **5% or more.**
- Include in the discussion the positive effects of reducing the risk of ovarian (and in some cases breast cancer) and the negative effects of a surgically induced menopause.
- Defer risk-reducing bilateral salpingo-oophorectomy until females have completed their family.

Contraindications to risk-reducing surgery for people with a personal history of breast cancer

- Do not offer risk-reducing surgery to people with comorbidities that would considerably increase the risks of surgery.
- Do not offer risk-reducing surgery to people who have a limited life expectancy from their cancer or other conditions.

Pre-implantation genetic testing (PGT)

Some high-risk pathogenic variant carriers (both female and male) might consider the option of Preimplantation Genetic Testing (PGT) to avoid passing the variant onto their children. PGT is a process that involves 'in vitro fertilisation' (IVF) to create embryos from the couple in the laboratory, which are then tested at an early stage for the familial variant. Access to PGT is through the Clinical Genetics Service and only where PGT eligibility criteria are met.

Insurance and genetic test results

In 2018 the Association of British Insurers agreed to an open-ended moratorium which means unaffected carriers of a pathogenic variant will not have to disclose the results of their predictive genetic test if taking out life or critical illness insurance after genetic testing. The Moratorium will be reviewed by the Department of Health and the ABI every 3 years.

Those who are having genetic testing as part of their diagnostic process (e.g. a breast cancer patient) would be having a diagnostic genetic test. Insurers can use this to inform subsequent applications for life or critical illness insurance. However, the key element of insurance evaluation is likely to be a cancer diagnosis, rather than at-risk status.

Guidelines, References & Appendices

UKCGG management guidelines for gene carriers

The UK Cancer Genetic Group have developed guidelines(https://www.ukcgg.org/information-education/ukcgg-leaflets-and-guidelines/) for the following gene carriers

- BRCA1
- BRCA2
- PTEN
- PALB2

Horizon scanning

- Consider screening for mod risk age 50 – 60 – SEE NICE Guidelines

References

NICE CG164 (https://guidance.nice.org.uk/cg164)Familial breast cancer(https://guidance.nice.org.uk/cg164): 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 Issued: June 2013

PHE Protocols for surveillance of women at very high risk of developing breast cancer - GOV.UK (www.gov.uk)(https://www.gov.uk/government/publications/breast-screening-higher-risk-women-surveillance-protocols/protocols-for-surveillance-of-women-at-higher-risk-of-developing-breast-cancer)

PHE Tests and frequency of testing for women at very high risk - GOV.UK (www.gov.uk) (https://www.gov.uk/government/publications/breast-screening-higher-risk-women-surveillance-protocols/tests-and-frequency-of-testing-for-women-at-very-high-risk--2)

HIS Familial breast cancer report (healthcareimprovementscotland.org) (https://www.healthcareimprovementscotland.org/our_work/standards_and_guidelines/familial_breast_cancer_report.aspx)

UK Cancer Genetics Group (2018) Consensus for genes to be included on cancer panel tests offered by UK genetics services. Authors: Amy Taylor,1 Angela F Brady,2 Ian M Frayling,3,4 Helen Hanson,5 Marc Tischkowitz,1,6 Clare Turnbull,7,8,9 Lucy Side,10 on behalf of the UK Cancer Genetics Group (UK-CGG)

The Manchester Scoring System (MSS) allows the calculation of the probability for the presence of mutations in the BRCA1 and BRCA2 genes in families suspected of having hereditary breast and ovarian cancer. (Evans et al, 2004)

Reference: Evans DG et al, 2017. Pathology update to the Manchester Scoring System based on testing in over 4000 families. J Med Genet 54: 674-681

Appendices

Manchester Scoring System(/national-cancer-management-pathways-under-development/breast-cancer/scottish-familial-breast-cancer/manchester-scoring-system/)

Author(s):

TBC

Version:

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Reviewer Name(s):

Frances Yuille