Breast Cancer Genetic Testing Pathway

Frequently Asked Questions

Section 1: Questions about the referral pathway

Q1.1: Why are patients under 31yo referred to the regional genetics centre for testing, rather than being tested by the local MDT?

These very young patients may have mutations in genes other than BRCA1/BRCA2/PALB2/CHEK2/ATM, which need to be requested by the regional genetics service. These women will be seen by the regional genetics service within 2 weeks of receiving the referral letter.

Q1.2: Are the broadened eligibility criteria applicable retrospectively (for patients diagnosed with breast cancer in the past)?

- There is no plan to offer testing retrospectively.
- Historically, the high-probability families will have been referred to the regional genetics service, so the pick-up rate from retrospectively testing patients, who were not eligible previously but are eligible now, will be very low.
- If a patient is eligible, but there has been a negative test in family over 10 years ago, the case should be discussed with the regional genetics team, to see if it is worth repeating the test.
- If a patient who has had breast cancer in the past re-presents to a breast unit, is eligible for testing, and has not had any prior testing, then testing can be offered.

Q1.3: How do I ensure I complete the request form correctly?

- Please use this referral form:
  Click here: NW GLH Genomic Testing Request Form – Rare Disease
  - Print and complete the form to accompany the blood sample and deliver to:
    North West Genomic Laboratory Hub – Manchester Site
    Manchester Centre for Genomic Medicine
    Sample reception 6th Floor
    St Mary's Hospital
    Oxford Rd
    Manchester
    M13 9WL
- Completing the form:
  - *Clinical Indication Code*: enter **R208** (for the BRCA1, BRCA2, PALB2, CHEK2 and ATM test). Please use the test code rather than writing out the genes that will be tested.
    For patients age 31-35 years, with triple positive (ER positive, PR positive, HER2 positive) disease, use clinical indication codes **R208 AND R216**, so that TP53 mutations are also tested for.
  - *Test Code:* **R208** (for the BRCA1, BRCA2, PALB2, CHEK2 and ATM test) and **R208** & **R216** for patients aged 31-35 years with triple positive disease.
  - *Clinical Details (type of test):* tick 'Diagnostic Test'.
  - Then document the patient's eligibility criteria e.g. *'Patient recently diagnosed with breast cancer. Eligible for genetic testing as patient has triple negative breast cancer under 60 years.'*

Q1.4: What about patients that do not want the test but would like to store their DNA sample for their family to access in the future?

Some patients do not consent to have the genetic test but do choose to have their DNA sample stored to give their blood relatives the option to access this at a later date. In these circumstances, the sample would not be tested within that person's lifetime but could provide information for other family members in the future. In this situation the consent form does not need to be completed.

The referral form must be completed as follows:

- Clinical Details (type of test) – tick DNA Storage.
- Clinical Indication Code/Test Code: R346 DNA storage only.

Further guidance on the North West Genomic Laboratory Hub can be found here: https://mft.nhs.uk/nwglh/

Q1.5: The algorithm recommends a 5-year review for patients found to have a variant of unknown significance (VUS). How do I arrange this?

It is recommended that patients with VUS are flagged for a 5-year VUS review, using InfoFlex, or an alternative software tracking tool, through the local breast team's aftercare programme (for example Personalised Stratified Follow Up programme).

Once a patient qualifies for VUS review at 5 years, please contact the Genomic Laboratory Hub using this email address: mft.genomics@nhs.net

Q1.6: What should I do if a patient has a negative germline mutation test result and is not eligible for referral to the regional genetics centre, but I am still concerned about their family history?

A regional cancer genomics MDT is held on the first Tuesday of the month at 11:00. Clinicians from around the region can request discussion of complex cases, for example, those with an unusual family history or if a clinician has questions about a test result.

If you wish to discuss a patient in more detail with the team please email: mft.nwglh-mdt@nhs.net

Family members of young patients with breast cancer and a negative result/VUS, should still be referred to **local** family history clinic for consideration of additional surveillance.

For further information about appropriate referrals to local family history, please see this link: https://www.nice.org.uk/guidance/cg164/chapter/Recommendations#care-of-people-in-secondary-care-and-specialist-genetic-clinics

Q1.7: For patients who require referral to the regional genetics centre, how long will they have to wait for their appointment?

Patients referred urgently are generally seen within 2-4 weeks, this would be the case for patients diagnosed with breast cancer under 31 years and for patients with breast cancer where genetic results would affect surgical/radiotherapy/SACT management.

Individuals referred for a routine appointment in the genetics cancer clinic will be seen within 3 months. The waiting time may be longer if you have specifically requested an appointment in one of the genetics outreach clinics at a local hospital.

Section 2: General questions about genomics and inherited breast cancer

Q2.1: What is the difference between germline and somatic mutations?

There are two ways in which gene mutations increase the risk of an individual developing cancer:

Somatic mutations occur in the genes of an individual cell and when that cell divides there is a risk of cancer development. Somatic mutations are not present when a child is conceived; they are acquired during the individual's lifetime. Smoking, aging, ultraviolet radiation and viruses are examples of causes of somatic mutations. Somatic mutations can be important in decision-making for cancer treatment and a patient's prognosis, but they are not hereditary.

Germline mutations are far less common than somatic mutations. They are inherited and therefore are present from the moment a person is conceived. Germline mutations can influence whether, and when, an individual might get cancer, what cancer they might develop and what treatments are appropriate and most likely to be successful.

The genetic test we offer eligible patients after a diagnosis of breast cancer, is a test for germline mutations in five genes: BRCA1, BRCA2, PALB2, CHEK2, and ATM. We also test the TP53 gene in patients under 31 years, and in patients aged 31-35 years who have triple positive disease. An error in one of these genes may result in an increased risk of developing cancer, particularly breast cancer.

It is important to remember that a very small number of cancers are caused by germline gene mutations. Although many families have multiple family members who have been affected by breast, ovarian and other cancers, most of these cases are caused by the combined effects of multiple genetic and environmental factors, with only about 5-10 % being due to an error in a single high risk cancer gene.

Q2.2: What are the CHEK2 and ATM gene errors that have been added to the standard R208 test in 2022?

CHEK2 gene error: An abnormal *CHEK2* gene can at least double the lifetime risk of breast cancer. It can also increase colorectal and prostate cancer risk.

ATM gene error: Inheriting two abnormal copies of the ATM gene causes ataxia-telangiectasia, a rare disease affecting brain development. Inheriting one abnormal ATM gene has been linked to an increased risk of breast and pancreatic cancer.
A patient with an ATM gene error has approximately a 17-30% chance of developing breast cancer over their lifetime. However, there is also a particular mutation affecting a specific location on the ATM gene where the lifetime risk of breast cancer may be much higher.

Q2.3: Why does the algorithm recommend referral to the regional genetics centre if the patient has a family history of:

- **Bowel cancer or polyps under 50 years of age**
- **Endometrial cancer under 50 years of age**
- **Thyroid cancer under 40 years of age**
- **Sarcoma at 45 years of age or under**
- **Diffuse gastric cancer?**

Apart from BRCA1, BRCA 2 and PALB2 gene mutations there are other inherited disorders that can increase the risk of breast cancer. These include:

- ***PTEN gene error (Cowden's syndrome):***
  This gene error results in an increased risk of breast, thyroid and endometrial cancer, as well as benign growths in the skin and small and large intestine.
  Women are at increased risk of benign breast conditions, such as ductal hyperplasia, papillomatosis, fibrocystic breast disease, and fibroadenomas.
  The lifetime breast cancer risk for women with a *PTEN* mutation is estimated at 25% to 50%.
- ***TP53 gene error (Li-Fraumeni syndrome):***
  This gene error results in an increased risk of breast cancer and several other cancers, including leukaemia, brain tumours, and sarcoma.
  Individuals with Li-Fraumeni syndrome have an approximate 54% risk of developing breast cancer by age 70.
- ***CDH1 gene error:***
  An abnormal *CDH1* gene increases the risk of a rare type of stomach cancer (diffuse gastric cancer). Women with an abnormal *CDH1* gene have a 39% to 52% lifetime risk of lobular breast cancer.
- ***STK11 gene error (Peutz-Jeghers syndrome):***
  An abnormal STK11 gene causes mucocutaneous pigmentation and gastrointestinal polyposis. The lifetime cancer risk is reported to be as high as 90%, including breast, colorectal, and pancreatic malignancies. In women with Peutz-Jeghers syndrome, the lifetime risk of breast cancer is estimated to be about 45%.