Northern Ireland Regional
Molecular Diagnostic Service

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Germline genetic testing for Breast Cancer patients (R208 & R444.1)
Frequently asked questions

This information is targeted at healthcare professionals who will be involved in requesting germline genetic tests for diagnostic purposes

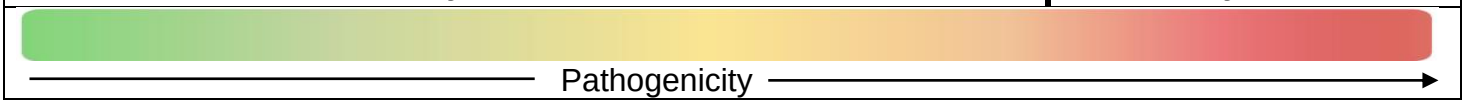
Version last updated May 2024

Background information- variants and terminology

When we talk about 'pathogenic variants' or 'likely-pathogenic variants' we are referring to those that are clinically actionable. Various terms can be used to describe pathogenic or likely pathogenic variants, including 'spelling change', 'gene alteration' or 'gene change'. In the past these were also commonly referred to as 'mutations', however in our team the current practice is to use the term '**pathogenic variant**' which is therefore used throughout this document.

It is also important to remember that there is a large amount of benign variation in our genetic material, that is not disease causing. Variants are classified depending on the degree of evidence to support their clinical significance and clinical actionability. For example, 'likely-pathogenic' refers to variants for which there is a 90% chance of pathogenicity.

Variant classification				
Benign	**Likely-benign**	**Uncertain significance**	**Likely-pathogenic**	**Pathogenic**
>99% certainty benign	>90% certainty benign	Lack of evidence at present to determine the variant's clinical significance	>90% certainty pathogenic	>99% certainty pathogenic
Not clinically actionable			**Clinically actionable**	



1. Who can offer germline genetic testing for breast cancer patients?

In addition to those within Genetic Medicine, these tests can be undertaken in a mainstream setting by:

- Consultant oncologist
- Consultant breast surgeon
- Other healthcare professionals who have the appropriate competency (supported by a competent consultant from one of the specialties listed above)

All testing criteria forms must have a **named consultant** listed in the appropriate section. Results will be returned to this consultant, even if testing has been requested by another member of their team. Referrals without a named consultant listed will be **refused**. It is also very important to include your **email address** on the referral form to allow for any further contact if required regarding the patient or test request.

2. What training is required for healthcare professionals to offer genetic testing?

In line with other genetics services there is no specific formal training requirement for mainstream clinicians offering diagnostic genetic testing for patients affected by cancer. Many clinicians will already have gained the required competency through a mixture of prior training and clinical experience. We are continuously developing new materials to support this.

In addition, a variety of online resources for patients and healthcare professionals can be found on **page 12-13** of this document. The Genetic Medicine service welcome contact from any healthcare professional who would like additional training or further discussion about their competency. Please contact genetic.medicine@belfasttrust.hscni.net to arrange this.

3. When should discussions about genetic testing be undertaken following a cancer diagnosis?

This should be at the discretion of the treating clinician. Genetic testing can be discussed and undertaken at the time of diagnosis, during active cancer management or during follow-up. It is important to note that patients undergoing cancer treatment may find discussing genetic testing and a potential risk to family members to be distressing at this time. Others may feel motivated to understand more about the cause of their condition for themselves and to inform potentially at-risk family members.

Genetic testing for patients where results will impact near clinical management such as surgical management or treatment **should be clearly stated on the panel request form in the appropriate section** to allow for sample management.

4. Which breast cancer patients are currently eligible for testing through mainstream teams?

- Breast cancer (including high grade DCIS) **<40**
- Bilateral Breast cancer **<50**
- Triple-negative breast cancer (ER-/PR-/HER2-) **<60**
- Male breast cancer **(any age)**
- Breast cancer **<45 AND** one or more first-degree relative with breast cancer **<45**
- Breast Cancer and Ashkenazi Jewish ancestry***** (**any age**)
- **Pathology Adjusted** Manchester Score **≥15** (family history including age(s) at diagnosis must be recorded on the panel request form)- those without will be refused

Up to date eligibility criteria can be found in the English National Genomic Test Directory
https://www.england.nhs.uk/wp-content/uploads/2018/08/Rare-and-inherited-disease-eligibility-criteria-version-6-January-2024.pdf

***** *It is important to ask about a patient's ethnicity/ancestry- those with breast cancer from Ashkenazi Jewish ethnic backgrounds have an increased chance of carrying a pathogenic variant in BRCA1/2.*

****** Patient ethnicity should be noted on all blood collection forms as this may alter the testing strategy utilised by the lab ******

5. Does breast cancer testing eligibility include those *in situ*?

When assessing a patient's genetic testing eligibility, high grade DCIS (ductal carcinoma in situ) should be considered in the same way as invasive breast cancers are.

6. Is testing available for patients who don't meet above criteria but would be eligible for PARP inhibitor therapies?

Yes, criteria for this is detailed below- there is a separate panel request form to request this '*R444.1 testing for the purpose of NICE approved PARP inhibitor treatment'* (on our website), and the criteria that the patient meets must be selected.

Note that this testing criteria **only applies to patients not meeting standard R208 criteria above**, AND **with a current cancer diagnosis for treatment decisions**.

- The same gene panel will be used for all patients

Criteria *(from the English 'National Genomic Test Directory' *)*

1) **For people with triple negative breast cancer who have received neo-adjuvant chemotherapy:**

• residual invasive cancer in the breast, the resected lymph nodes (non-pathological complete response) or both at the time of surgery

2) **For people with triple-negative breast cancer having adjuvant chemotherapy:**

• node-positive OR
• node-negative cancer with a primary tumour ≥ 2 cm

3) **For people with hormone receptor-positive, HER2-negative breast cancer who have received neoadjuvant chemotherapy:**

• residual invasive cancer in the breast, the resected lymph nodes (non-pathologic complete response) or both at the time of surgery, AND a CPS + EG score of ≥3 based on pre-treatment clinical and post-treatment pathological stage, receptor status and histological grade

4) **For people with hormone receptor-positive, HER2-negative breast cancer having adjuvant chemotherapy:**

• 4 or more pathologically confirmed positive lymph nodes.

* *https://www.england.nhs.uk/wp-content/uploads/2018/08/Rare-and-inherited-disease-eligibility-criteria-version-6-January-2024.pdf*

7. Which additional patients may be offered testing are offered testing via the Genetics service?

- CanRisk score **≥10%***

In addition, genetic testing may occasionally be appropriate through the Genetic Medicine Service outside these criteria in exceptional circumstances, following discussion and agreement at an MDT with a cancer geneticist present. Examples of such patients circumstances include:

- **Living affected individual with pancreatic cancer** AND family history of breast/high grade ovarian/prostate cancer with a pathology adjusted Manchester score of ≥ 15/CanRisk score of 10%.
- **Living affected individual with prostate cancer** AND a family history of breast/ovarian/pancreatic cancer with a pathology adjusted Manchester score of ≥ 15/CanRisk score of 10%.
- **Deceased affected individual** with breast* or high grade ovarian cancer with:
  - A stored DNA, blood or tissue sample available for DNA extraction, AND Pathology-adjusted Manchester score ≥17 or CanRisk score ≥15%, AND
  - No living affected individual is available for genetic testing
- **Living unaffected** individual with:
  - First degree relative affected by breast* or serous ovarian cancer, AND
  - Combined pathology-adjusted Manchester score ≥20 or BOADICEA/CanRisk score of ≥20% for affected relative or BOADICEA/CanRisk score of ≥10% for unaffected relative AND
  - No living affected individual is available for genetic testing, AND
  - No deceased affected individual with tumour material available for testing

Patients who meet any of these additional criteria should be referred to the Genetic Medicine service for a review, via **genetic.medicine@belfasttrust.hscni.net**.

If results are **required for clinical management** such as surgical or treatment choices, please send a blood sample requesting DNA storage and discuss with the on-call genetic counsellor who can be reached (Monday-Friday, 9-5) via phone 02895 048022**,** or the above email.

If the patient has a significant additional family history of cancer suggestive of another cancer predisposition such as PTEN Hamartoma Tumour syndrome or Li-Fraumeni syndrome (TP53), but does not meet any of the above testing criteria, we will be happy to discuss this with you and review their family history.

*Information is provided later in this document about how to calculate CanRisk (**page 14**) and Manchester (**pages 14-16**) scores.*

8. How do I choose which panel is most appropriate for my patient?

All patients who meet the above testing criteria are now offered a multi-gene breast and ovarian cancer panel test. Although BRCA1/2 are still responsible for the majority of inherited breast and ovarian cancers, additional genes that increase an individuals' risk of developing these cancers have been identified. Therefore, by offering testing of these additional genes alongside BRCA1 and BRCA2, the **overall diagnostic rate is increased** and there is a greater chance of finding any causative gene variants. It is important to note that many genes included in the test are associated with risks of other cancers.

Family history should be clearly noted in the referral, and this information is considered in the reporting of the genetic test result.

9. What are the additional genes on the 'Inherited Breast and Ovarian Cancer Panel'?

The **breast and ovarian cancer panel** includes ATM, BRCA1, BRCA2, BRIP1, CHEK2, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53. This panel test includes genes associated with Lynch syndrome (underlined). Further information about the genes included in the panel, their associated risks, and screening recommendations can be found on **page 17** of this document.

10. Will any other genes be tested?

If the patient has a significant family history of other cancers, please seek advice from Cancer Genetics on whether further testing is required. A patient blood sample and consent should be taken as normal, but contact should made with the genetics team via 028 9504 8022 or genetic.medicine@belfasttrust.hscni.net to review the family history before the laboratory analysis begins. This is to ensure that the most appropriate test is applied.

11. If a patient has a family history of a BRCA1/2 or other pathogenic variant, but is eligible for a panel test, which is most appropriate?

If there is a known cancer predisposing pathogenic variant in the family that has already been identified through genetic testing, the first logical step is typically to request a **targeted genetic test,** to look for this specific variant, rather than panel testing. The likelihood of your patient having inherited the familial pathogenic variant is much greater than the likelihood of a different pathogenic variant associated with breast cancer being present in the family. This type of testing will have a faster turnaround time.

If possible, a blood sample should be taken along with details of the family member who has already been tested (e.g. full name, DOB, H&C no, or their Northern Ireland genetics reference number if known). It is important that you then **contact the on-call genetic counsellor** to ensure that no other testing is required.

12. What do we mean by 'family history'?

Family history refers to first, second, and third degree relatives of the patient:

	DNA shared	Examples of relatives
First-degree	50%	Parent, full-sibling, or child of the patient
Second-degree	25%	Aunt, uncle, grandparent, grandchild, niece, nephew, half-sibling of patient
Third-degree	12.5%	First-cousin, great grandparent/grandchild, great aunt/uncle, great niece/nephew

13. What if a patient meets criteria but chooses not to have a test, is undecided, or requires additional time to reach a decision?

Having genetic testing is an entirely personal decision, and is not mandatory. Whether or not an individual chooses to be tested is often based on a combination of unique personal and circumstantial factors. If a patient declines genetic testing, it is important to make them aware that the option remains open to them if they change their mind in the future. **Please do not hesitate to refer individuals to Genetics if they require a more detailed discussion about the process.**

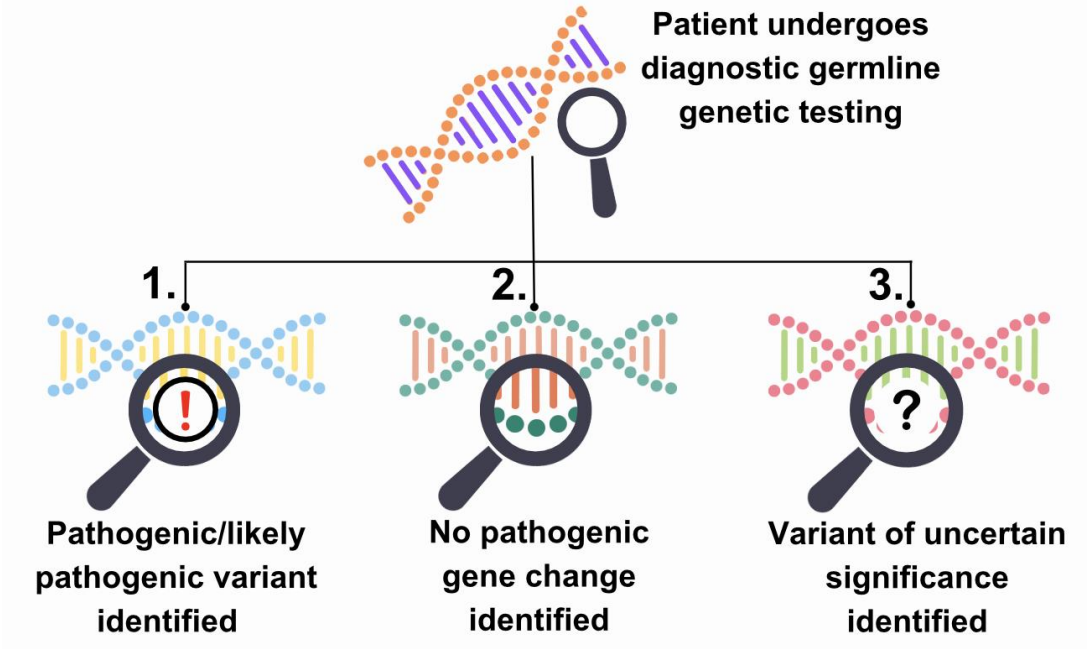
If the above applies to any patients for whom there may be urgent treatment or management decisions based on genetic testing, contact the on-call genetic counsellor to discuss whether a rapid clinic appointment could be facilitated for them.

14. If my patient is having palliative care but is not eligible for genetic testing or chooses not to have it at this time, can DNA be stored?

We would welcome DNA samples being stored for any patients who are undergoing palliative care, where their personal or family history suggests that genetic testing may be of benefit for their relatives in the future. Complete the standard blood collection form and clearly note on it that the sample is for storage rather than for testing. Please make family members aware that this has occurred and that they can seek a referral through to the genetics service in the future for a family history assessment +/- testing if they meet criteria.

15. What are the possible outcomes of genetic testing?

There are **three possible outcomes** of genetic testing. All should be discussed with patients prior to initiating the test to prepare them for the possibility that genetic testing may not yield any significant findings, and can also yield results that are uncertain or unexpected.



1) **A pathogenic (disease-causing) or likely-pathogenic variant is detected** in one of the genes analysed, and provides an explanation for the patient's cancer diagnosis. This result may help to guide future treatment, care, and management decisions. Even if there are no practical changes in terms of care, a genetic diagnosis can still have a significant impact in helping patients to understand their cancer risks. Depending on which gene the change was found in, this result can inform patients that they have increased risks of developing other primary cancers. It also has implications for certain blood relatives, who (depending on age and relation to the patient) may be offered testing via their local clinical genetics service to determine whether they also carry the same pathogenic variant.

2) **No pathogenic or likely pathogenic change is detected in any of the genes analysed:** This result does not change the patient's clinical diagnosis, but means that the reason why this patient developed cancer remains unknown based upon existing scientific knowledge. This result reduces the likelihood, but does not exclude the possibility that there is an underlying genetic basis for the patient's cancer. There is still a small chance that there is a pathogenic change in another cancer predisposition gene that was not included in the panel test. If a patient receives this result, but has a strong cancer family history, they may contact their GP or local family history clinic to discuss whether further input from the genetic service is required. Depending on the family history, screening may still be available to help manage the cancer risk for relatives.

3) **A variant of uncertain significance (VUS) is detected:** These are reported in a small number of patients. This result means that a change has been detected in one of the genes in the panel, but it is not clear at present if the change is disease-causing and relevant to the patient's diagnosis, or is benign and just part of natural human variation. Although a conclusion cannot be reached at this time, the patient's data may be reviewed in the future (e.g. based on changes to their clinical or family history, or in light of new scientific information), which may change the interpretation of their VUS. These results cannot be used to inform treatment or risk for family members at that point in time, and screening recommendations should be based on family history. We would recommend that patients with a VUS are referred to Cancer Genetics for further discussion.

16. How should I explain genetic testing to patients?

Below is a suggested brief step-by-step outline in plain English which outlines the key points about genetic testing to explain to patients:

a) The genetic test is a blood test

b) It will check whether you have a fault (change) in a number of genes which are known to cause an increased risk of breast cancer as well as other cancers

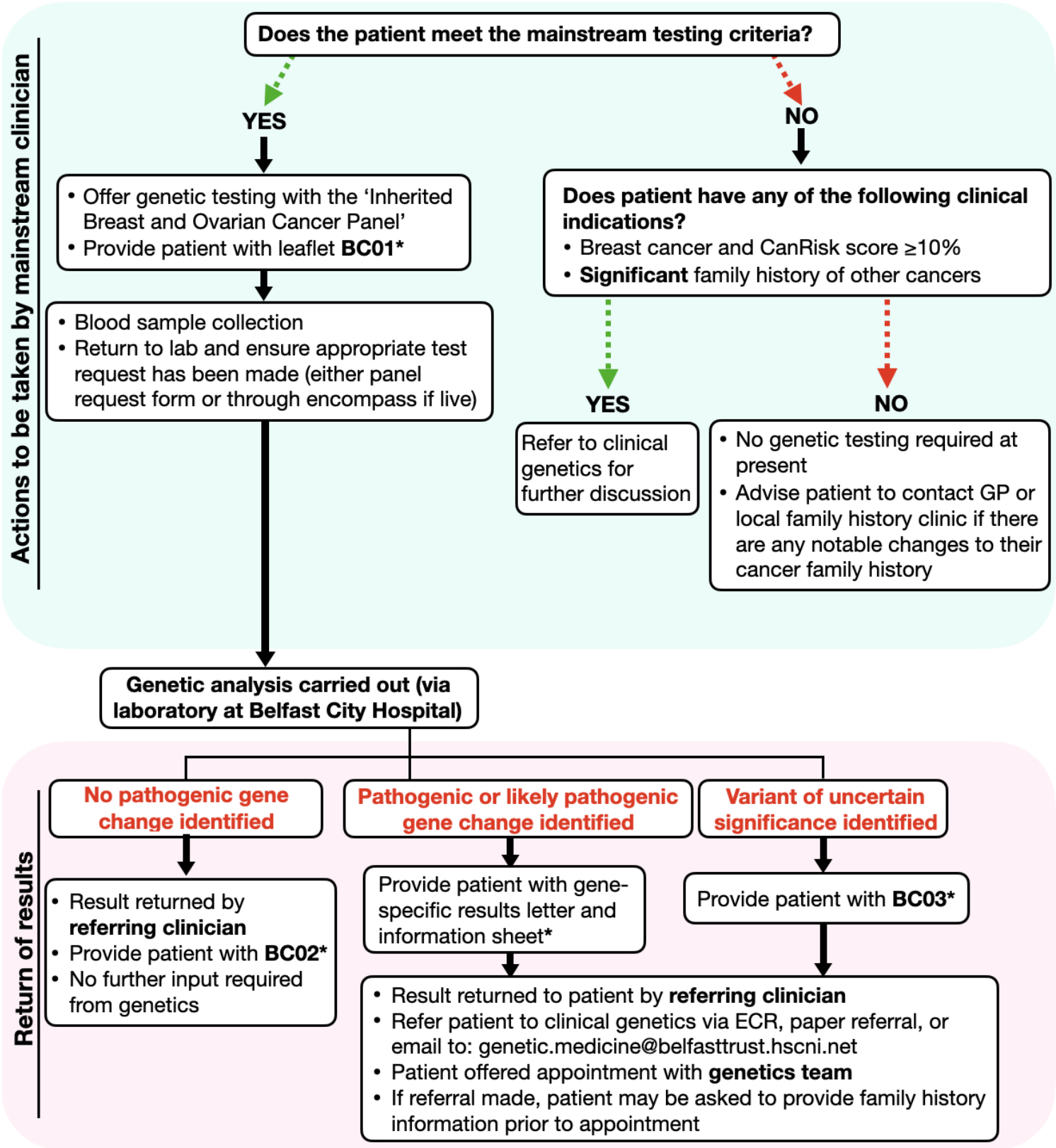
c) For most patients without a family history of cancer, the result is that no variants are identified. This is reassuring for your family members as it means your cancer is less likely to be hereditary.

d) If we identify a pathogenic (disease-causing) variant in a cancer predisposition gene it may help guide your cancer treatment and future management options. It will also mean your relatives could also carry the same pathogenic variant, and they would be offered the same test to find out if they have any increased cancer risks.

e) Some test results give an uncertain result, known as a 'variant of uncertain significance'. This means that it is not clear whether the pathogenic variant identified is disease-causing, or just part of normal human variation.

f) If the result identifies a disease-causing change or an uncertain result in one of the genes tested, you will be referred to the genetics team for further discussion about the implications of this result for yourself and your family.

You may find it useful to use this protocol when assessing whether your patient is eligible for genetic testing:



***** All leaflets (BC01-BC03) and documents referred to above can be found in the '**Patient information leaflets**' section at:
https://belfasttrust.hscni.net/service/laboratory-services/clinical-genetics/mainstreaming-cancer-genetics/breast-cancer-mainstreaming/

17. Are there any other important considerations to address when discussing genetic testing with patients?

Eliciting expectations: prepare patients for possible results and the fact that this test may not provide an underlying cause for their diagnosis or may reveal additional cancer risks.

Purpose/scope of the test: looks at genes associated with their clinical condition only. This also includes outlining the relevance of that test for the patient and/or their family members, given their clinical situation.

Implications for the wider family: the results of genetic testing may be used for the benefit of family members. For example, if a pathogenic variant is identified in a patient, their at-risk relatives may be offered predictive testing and options to help manage their own risk if appropriate.

Acknowledging uncertainty: there may be uncertainty about the genetic changes found in patients, as described on page 7.

Establishing a follow-up plan: ensure patients are aware of the timeframe by which they can expect a result, how they will be contacted about their results, and by whom.

18. What tubes should blood be collected in for genetic testing?

4-8mls of blood should be collected in EDTA (purple top) tubes. Please send the blood sample to the Regional Molecular Diagnostic Service, Belfast City Hospital. This must be accompanied by the standard genetics consent/ blood collection form and the R208 panel testing criteria form in the same poly pocket *(both available at:* https://belfasttrust.hscni.net/service/laboratory-services/clinical-genetics/mainstreaming-cancer-genetics/breast-and-ovarian-cancer-mainstreaming/ *under the section 'Breast cancer test request form').* If you require copies of either of these forms, contact the clinical genetics service via email for this to be arranged.

19. What are the key things to discuss when taking patient consent?

- Testing is for diagnostic purposes and only the genes listed on the panel will be analysed.
- Normal laboratory practice is to store the DNA extracted from the sample even after the current testing is complete. The sample might be used as a 'quality control' for other testing, for example, that of family members.
- Results will be stored electronically as part of their healthcare record.
- Results may be open to future interpretation, e.g. in light of new scientific information.

20. What happens once my patient has had blood taken for genetic testing?

The blood sample will be sent directly to the laboratory (**The Regional Molecular Diagnostics Service- Belfast City Hospital**), and testing may be carried out within this laboratory or an external accredited provider. The result will be returned to the requesting clinician. Currently, these are in paper form via post, however we are actively seeking alternative solutions, such as having these made available on ECR.

21. Who is responsible for returning results?

The referring clinician is responsible for returning their patients' result. Any patients who receive a pathogenic or VUS result should be referred to clinical genetics to discuss this. **Referrals can be made via post, ECR, or genetic.medicine@belfasttrust.hscni.net**. Please ensure you provide correct patient contact details with all referrals.

There are information sheets specific to each possible result on the 'Mainstreaming cancer genetics page' our website- patients should be provided with whichever is relevant to themselves only.

22. What is the turnaround time for receiving results?

Results for diagnostic genetic testing will generally be available in around 12 weeks. Occasionally there are unavoidable delays in the laboratory.

Patients should be made aware of the above timeframe at the time of testing.

23. What is discussed at a follow-up genetics appointment for patients found to have a pathogenic or likely-pathogenic variant?

If a clinically actionable variant is found in any of the genes tested, the patient will be offered a follow-up appointment with clinical genetics (typically 2-3 months after receiving result). If you feel your patient needs to be seen more urgently than this, please contact the on-call genetic counsellor and we will try to facilitate this.

Prior to their appointment they may be asked to provide **family history information**. This is to allow us to:

- Identify any at-risk relatives who should be offered testing
- Provide tailored risk information to be provided (for some breast and ovarian cancer predisposition genes, the associated risks vary significantly when family history and individual circumstances are considered)

During their appointment they will receive tailored information about:

- Possible implications of their result e.g. their risks of developing further primary cancers
- Ways to manage their personal risks (additional screening and

management recommendations)
- Details about how at-risk relatives can self-refer to clinical genetics
- Where to access support and reliable information sources
- Research studies they may be eligible to participate in based on result: e.g. patients with pathogenic variants in BRCA1, BRCA2, RAD51C, RAD51D, BRIP1 or PALB2 are currently being recruited at Belfast City Hospital for the following study: Preventing ovarian cancer through early excision of tubes and late ovarian removal (**PROTECTOR**) http://protector.org.uk/information-for-health-professionals/

24. Further questions?

Please contact the Genetics Team via email at: genetic.medicine@belfasttrust@hscni.net. You can also reach us by telephone 9am-5pm Monday to Friday via 028 9504 8022 and ask to speak with the on-call genetic counsellor.

We gratefully acknowledge both the St Georges and Nottingham cancer genetics teams. This FAQ document was adapted from those developed for their services, with their consent.

Useful resources for patients

It is also helpful for healthcare professionals to be aware of additional information resources and support options available to patients, and how to direct them to these.

Please also see our website for the most up to date resources and documents: https://belfasttrust.hscni.net/service/laboratory-services/clinical-genetics/mainstreaming-cancer-genetics/breast-and-ovarian-cancer-mainstreaming/

Belfast trust booklet- Diagnostic testing for hereditary breast and ovarian cancer: can be found on our website (link above) under the 'patient information leaflets' section (physical copies can be requested through clinical genetics).

Information sheets explaining different types of results- can be found on our website (link above) under the 'patient information leaflets' section.

BRCA link NI: http://brcani.co.uk/about.html An organisation helping people with Hereditary Breast and Ovarian Cancer access information and support. They organise group meetings and formal events with guest speakers.

Macmillan cancer- 'Cancer genetics - how cancer sometimes runs in families' booklet: https://www.macmillan.org.uk/cancer-information-and-support/stories-and-media/booklets/cancer-genetics-how-cancer-sometimes-runs-in-families

Macmillan cancer- 'Family history, genetics and cancer risk' webpage https://www.macmillan.org.uk/cancer-information-and-support/worried-about-cancer/causes-and-risk-factors/family-history-genetics-and-cancer-risk?_ga=2.146798900.1274912087.1682079499-456418398.1682079499

Breast Cancer Now booklet: 'Family history of breast cancer: managing your risk' booklet: https://breastcancernow.org/information-support/publication/family-history-breast-cancer-managing-your-risk-bcn244

National Hereditary Breast Cancer Helpline: https://www.breastcancergenetics.co.uk

Together in Surgical Menopause is a UK-based patient-led resource for those experiencing surgical menopause, for example due to risk-reducing removal of the ovaries.
http://www.surgicalmenopause.co.uk/index.html

Useful resources for healthcare professionals

UK Cancer Genetics group website leaflets and guidelines section: UKCGG leaflets and guidelines – Cancer Genetics Group

Contains management guidelines for **BRCA1, BRCA2, BRIP1, PALB2, RAD51C, RAD51D, PTEN** germline pathogenic variant carriers.

Genomics 101 Series- 'Genomics in Healthcare' e-learning course: https://portal.e-lfh.org.uk/Component/Details/540918 Targeted at healthcare professionals working in the NHS who have had limited exposure to genomics in their clinical role- covers introductory information and how is applied in healthcare.

NHS Genomics Education Programme- 'Facilitating Genomic Testing: Introduction to Offering Genomic Tests' e-learning course: https://www.genomicseducation.hee.nhs.uk/education/online-courses/facilitating-genomic-testing-introduction-to-offering-genomic-tests/ (~30 mins) Developed for healthcare professionals working in the NHS who will be involved in requesting genetic tests for patients. Individuals accessing this course are expected to already have a fundamental understanding of genomics.

British menopause society https://thebms.org.uk the BMS educates, informs, and guides healthcare professionals, working in both primary and secondary care, on menopause and all aspects of post reproductive health.

Risk assessment tools

Assessment tools routinely used in our assessment of cancer genetic patients include '**CanRisk'** and the '**Pathology Adjusted Manchester Score'.** Calculating these would not be expected of you, however, may help you to assess whether a patient who does not meet the mainstreaming test criteria would be eligible through the genetic service.

How to calculate a CanRisk score

CanRisk is a (free to access) comprehensive computer-based model that can be used by healthcare professionals to calculate the likelihood of carrying mutations in several moderate to high-risk genes, and an individual's future risks of developing breast and ovarian cancer. The website https://canrisk.org/ contains step-by-step instructions and training videos on how to calculate CanRisk scores.

In order to obtain an accurate output from CanRisk, a full family history is required. Therefore, we would recommend that if a CanRisk calculation is required for the patient to meet testing eligibility, **they should be referred to Clinical Genetics** where we can obtain and upload family history via our online family history system.

How to calculate the Pathology Adjusted Manchester Score

The Pathology- adjusted Manchester score (PAMS) score is calculated by adding up points for cancer diagnoses in a family according to the age at which individuals are affected. Importantly, **the score is adjusted according to the pathology of the breast or ovarian cancer in the person being tested.** Pathology from other relatives is **not required**. The PAMS scoring system is outlined on the following page. A combined score of ≥15 is required to offer genetic testing to those who do not meet standard criteria. If you would like further help in calculating a patient's score, please contact genetic.medicine@belfasttrust.hscni.net

Manchester Scoring System Information Sheet

The Manchester Scoring System (MSS) calculates the probability of mutations in the *BRCA1* and *BRCA2* genes in families suspected of having hereditary breast and ovarian cancer [1]

This information sheet provides a guide for non-genetic specialists to facilitate the calculation of a Manchester Score for patients with a new diagnosis of breast cancer.

Patients with a Manchester Score >14 are eligible for germline mutation testing

How to calculate the Manchester Score?

PART ONE – reviewing the patient's family history

- For each relative with cancer (including DCIS), assign a score based on the relative's age at diagnosis **(see table 1)**
    - If the exact age is unknown, use a best estimate. If there is no information on age assume the affected relative to be 60 years
- If a relative has had more than one primary cancer, assign a score for each cancer episode
    - These cancers must not be recurrences or secondary cancers
- Assess the maternal and paternal lineages as **two separate entities** - **do not add the scores from both sides of the family together**
    - Add up the scores for each affected relative with cancer on the maternal side
    - Add up the scores for each affected relative with cancer on the paternal side
    - If cancers occurred on both sides of the family, use the lineage with the highest score.
- Which relatives to include?
    - You can allow one intervening female relative unaffected by cancer in the calculation (i.e. include the score of a second degree relative with BRCA-associated cancer, when the associated female first degree relative is unaffected)
    - You can allow more than one intervening female relative, unaffected by cancer, if one of them has had risk reducing surgery at an age less than 50 (i.e. if a first degree relative had risk reducing surgery <50yo, an associated second degree relative was unaffected, and the third degree relative had BRCA-associated cancer, then the third degree relative should be included in the scoring)
    - Cancers through unaffected male relatives are counted (i.e. if the father is unaffected, but paternal grandmother had BRCA-associated cancer, then the grandmother should be included in the scoring)

PART TWO: Adjusting the score according to your current patient's tumour biology

 Once the total score (sum of all eligible relatives on the most affected side of the family) is calculated, adjust the score according to your **current patient's** tumour biology **(see table 2)**

Table 1: Scoring system for each member of your current patient's family

Gender of relative	Cancer	Age at diagnosis	Score	Calculation
Female	Breast Cancer	<30	11	
	Breast Cancer	30-39	8	
	Breast Cancer	40-49	6	
	Breast Cancer	50-59	4	
	Breast Cancer	>59	2	
Male	Breast Cancer	<60	13	
	Breast Cancer	>59	10	
Female	Ovarian Cancer	<60	13	
	Ovarian Cancer	>59	10	
Any gender	Pancreatic Cancer	Any age	1	
Male	Prostate Cancer	<60	2	
	Prostate Cancer	>59	1	
			Total	

Table 2: Adjustments according to your current patient's tumour biology

Patient's tumour biology	Adjustment to Manchester Score	Calculation
Triple negative tumour	+ 4	
ER positive and HER2 negative	-1	
ER positive and HER2 positive	-7	
ER negative and HER2 positive	-5	
Grade 3	+2	
Grade 1	-2	
DCIS only (no invasive disease)	-2	
Invasive lobular cancer	-2	
	Total	

References:
1.Evans et al, 2017. Pathology update to the Manchester Scoring system based on testing in over 4000 families. J Med Genet 54 (10): 674-681.

‘Inherited Breast and Ovarian Cancer’ panel genes

Panel gene	Typical cancer associations	Frequent screening advice (may be personalised based on family history and age)	Gene specific information page
ATM	c.7271T>G high breast cancer risk	Very high risk breast screening.	https://atsociety.org.uk/about-a-t/a-t-and-cancer/a-t-and-breast-cancer/
	All other pathogenic variants: breast cancer risk moderately increased	Moderate risk breast screening.	
	Biallelic (two) ATM pathogenic variants : high breast cancer risk	Very high risk breast screening.	
BRCA1	High breast & ovarian cancer lifetime risks	Very high risk breast screening. *	https://www.ukcgg.org/media/12257/ukcgg_brca1_guideline_finalv2_31032023_a4_pdf.pdf
BRCA2	High breast, ovarian and prostate cancer lifetime risks	Very high risk breast screening. Annual PSA test from age 40. *	https://www.ukcgg.org/media/12258/ukcgg_brca2_guideline_finalv2_31032023_a4_pdf.pdf
BRIP1	Increased lifetime ovarian cancer risk	Any breast screening based on family history alone	https://www.ukcgg.org/media/12261/brip1_final_-v1_31032023_a4_pdf.pdf
CHEK2	Moderately increased breast cancer risk (those with strong breast cancer family history may be high risk).	Moderate risk breast screening. Surveillance may be considered in the context of family history.	https://www.ukcgg.org/media/12387/ukcgg_chek2_guideline_version-1_06102023.pdf
EPCAM	Bowel and endometrial cancer, other cancer risks not well established	2-yearly colonoscopies 25-75, one-off H.pylori screen	https://www.facingourrisk.org/info/hereditary-cancer-and-genetic-testing/hereditary-cancer-genes-and-risk/genes-by-name/epcam/cancer-risk **
MLH1	Bowel, endometrial, ovarian and upper GI cancers, other smaller risks	2-yearly colonoscopies 25-75, one-off H.pylori screen	https://www.ukcgg.org/media/11601/mlh1-protocol-cgg.pdf
MSH2	Bowel, endometrial, ovarian, upper GI, renal, prostate and brain cancers	2-yearly colonoscopies 25-75, one-off H.pylori screen	https://www.ukcgg.org/media/11602/msh2-protocols-cgg.pdf
MSH6	Bowel, endometrial, ovarian cancers, smaller risks of upper GI, renal, brain	2-yearly colonoscopies 35-75, one-off H.pylori screen	https://www.ukcgg.org/media/11603/msh6-protocol-cgg-1.pdf
PALB2	High breast cancer risk & slightly increased ovarian cancer risk (higher in presence of family history of ovarian cancer).	Very high risk breast screening. *	https://www.palb2.org/wp-content/uploads/2021/11/Information-for-PALB2-Carriers-and-their-families-v1-NOV2021-1.pdf
PMS2	Bowel and endometrial cancer	2-yearly colonoscopies 35-75, one-off H.pylori screen	https://www.ukcgg.org/media/11604/pms2-protocols-cgg.pdf
PTEN	Very high breast cancer risk. Increased lifetime risks of renal, thyroid, endometrial, bowel, skin & brain cancers.	Very high risk breast screening. Surveillance available for thyroid, renal, bowel, skin cancer risks; brain MRI only if symptomatic.	https://www.ukcgg.org/media/12094/_media_10879_pten_management_-_cgg_4may2017-1.pdf
RAD51C	Increased breast & ovarian cancer risks (vary significantly when cancer family history & age are considered).	Breast screening recommendations will be made based upon individualised risk assessment.*	https://www.ukcgg.org/media/12229/rad51c-guideline-13122022.pdf
RAD51D			https://www.ukcgg.org/media/12230/rad51d-guideline-13122022.pdf
STK11	Increased risks of several cancers-primarily breast, ovarian, pancreatic & gastrointestinal.	Very high risk breast screening. *	https://www.facingourrisk.org/info/hereditary-cancer-and-genetic-testing/hereditary-cancer-genes-and-risk/genes-by-name/stk11/cancer-risk **
TP53	Wide spectrum of cancers & typically young onset e.g. breast, brain, adrenocortical, sarcomas & haematological malignancies.	Very high risk breast screening. Additional screening may be available on a research basis.	https://www.genomicseducation.hee.nhs.uk/genotes/knowledge-hub/heritable-tp53-related-cancer-syndromes/

*** No current screening programme for ovarian cancer risk**
**** American websites, screening and management guidelines may differ from those in the UK**