Breast Cancer Genetic Panel Testing

Training Document

21 November 2023
Version 3

Training Document Contents

1. Introduction

Up to 10% of breast cancers are thought to, at least in part, have a hereditary cause. Clinically significant germline variants in specific genes, such as BRCA1 and BRCA2, are identified in around 5% of breast cancer cases. Identifying clinically significant germline variants is increasingly impacting on treatment and surgical options. Additionally, identifying a genetic cause for the cancers in a family enables identification of other family members at risk.

We would encourage you to watch the following videos:

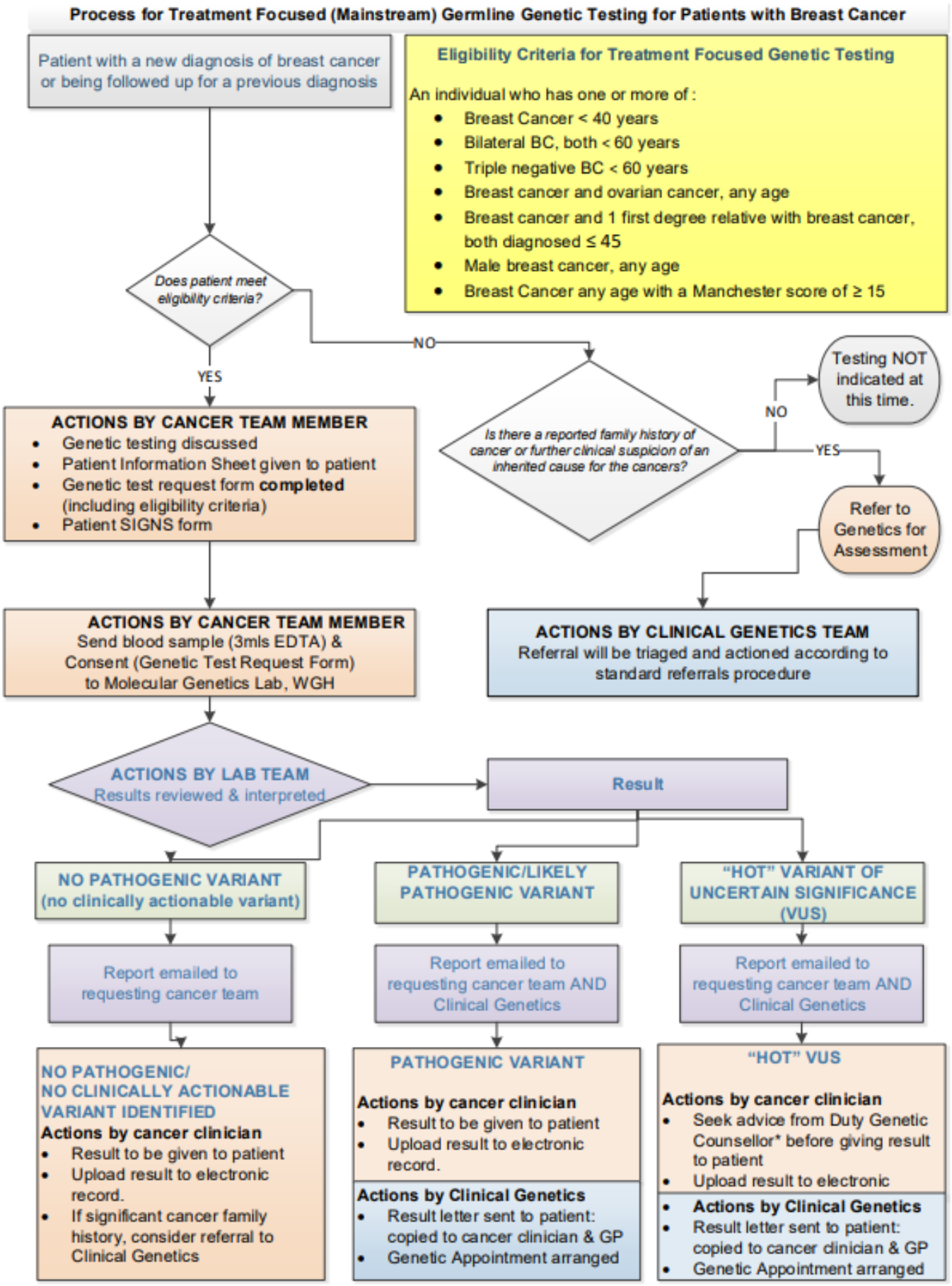
- Genetic Testing for Patients with Breast Cancer (eligibility, processes, consenting and practical aspects of sending samples)

- Germline Breast Cancer Panel Genetic Testing in Scotland (detailed information on the current genes included in the Breast Panel)

After watching these you should have a good understanding of the role of the breast cancer team in providing patients with genetic testing.

You will find in this document, the Current Process Flowchart, Frequently Asked Questions and additional relevant documents in the Appendices.

2. Protocol flowchart



3. Frequently asked questions

Which patients can have breast cancer genetic panel testing?

Non-geneticists can only undertake testing in breast cancer (BC) patients that fulfil one or more of the following criteria.

NHS patient with:

- Breast Cancer under 40 years
- Bilateral BC, both under 60 years
- Triple negative BC, under 60 years
- Breast cancer and ovarian cancer, any age
- Breast cancer and 1 First Degree Relative with breast cancer, both 45 years or under
- Male breast cancer, any age
- Manchester score of 15 or more* or a CanRisk ** variant probability of 10% or more

*Manchester score is used to factor in family history. More advice is provided later in the document however, you may wish to contact Clinical Genetics for advice regarding eligibility.
**https://www.canrisk.org

Referrals and queries about whether patients are eligible can be directed to wgh.clinicalgenetics@nhslothian.scot.nhs.uk

Which non-geneticists can perform genetic testing in eligible patients?

Non-geneticists who are registered healthcare professionals can request testing. Training materials have been developed to support competency development (this document, videos, and patient information leaflet).

What if my patient has further questions about the testing that I cannot answer?

Please contact the Clinical Genetics Service and ask to speak to the duty Genetic Counsellor to help clarify any questions. Alternatively, the patient can contact the Duty Genetic Counsellor directly. The contact details are available on the Genetic Testing for People Affected by Breast Cancer (Appendix 4.1) leaflet.

How were the eligibility criteria for breast cancer patients decided?

The current testing eligibility criteria were evaluated as part of the Edinburgh Mainstreaming Breast Cancer Testing Pilot and are available on the Scottish Genomic Test Directory: Rare and Inherited Disease.

What is the testing eligibility for private patients?

Any private patient with breast cancer who meets the described criteria and are eligible for NHS care, can be referred to Clinical Genetics. They cannot use this NHS mainstreaming process. Alternatively, the private provider can arrange for the patient to have testing through a private company (e.g.. www.genehealthuk.com or everythinggeneticltd.co.uk).

How strict are the age cut-offs for testing?

These are strictly applied. For example, a woman with bilateral breast cancer diagnosed at 58 years and 61 years (and no family history) would not be eligible for testing, but if she were diagnosed at 58 years and 59 years, she would be eligible. It is recognised, and inevitable, that individuals close to a threshold may have similar likelihoods of having a clinically significant variant but different eligibility. It is important for clinicians and patients to have confidence that criteria are being consistently applied.

If you think a patient is not eligible but might be eligible on the grounds of family history, you can contact Clinical Genetics and ask to speak to the on-call duty Genetic Counsellor or contact them via WGH.clinicalgenetics@nhslothian.scot.nhs.uk

How is triple-negative breast cancer defined?

A triple-negative breast cancer is defined as a tumour with an Allred score of 0, 1 or 2 for ER and PR receptors and HER2 negativity by IHC or FISH.

Should in situ breast cancer be included?

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 assessing eligibility for testing.

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 considered as separate cancers (i.e. counted as a bilateral breast cancer) when assessing eligibility for breast panel genetic testing, unless the second cancer is a recurrence. This is a pragmatic approach as it is not possible to robustly identify which are separate cancers and which are recurrences.

How should multiple synchronous ipsilateral breast cancers be assessed?

Simultaneous ipsilateral breast cancers, whether termed synchronous, multicentric or multifocal, should be counted as a single breast cancer for assessing eligibility for genetic testing.

What is the Manchester score?

The Manchester score is a scoring system that assesses an individual's diagnosis and their family history for the likelihood they have a clinically significant germline variant in BRCA1 or BRCA2. A Manchester score of 15 or more is estimated to equate to a 10% probability of carrying a clinically significant variant in BRCA1 or BRCA2 and is the agreed testing threshold in the UK. Detailed information on the Manchester scoring system can be read in the following paper: https://pubmed.ncbi.nlm.nih.gov/28490612/

The basic Manchester scoring system is shown below:

Cancer, age at diagnosis	Score
Female Breast Cancer, <30	11
Female Breast Cancer, 30-39	8

Female Breast Cancer, 40-49	6
Female Breast Cancer, 50-59	4
Female Breast Cancer, >59	2
Male Breast Cancer, <60	13
Male Breast Cancer, >59	10
Ovarian Cancer, <60	13
Ovarian Cancer, >59	10
Pancreatic Cancer	1
Prostate Cancer, <60	2
Prostate Cancer, >59	1

If there is any doubt over the diagnoses in a family, please contact the duty Genetic Counsellor to discuss.

When should discussion of genetic testing be undertaken?

This should be at the discretion of the clinician. Genetic testing can be discussed and undertaken at the time of diagnosis, during active cancer management or during follow up. However, please be aware that the lab result usually takes 8-10 weeks from receipt of sample, so if the result is required for management decisions, timing of testing must be planned accordingly.

NHS Scotland genetic testing resources are limited (e.g. lab staff and equipment) and shared across the needs of all genetic conditions and health specialties. Accessing genetic analysis in a timely manner is important to all. As a result, we request that you ONLY request the 4 week turn around where there is need for immediate management decision making.

What information leaflet should I give to the patient prior to obtaining consent?

The Genetic Testing for People Affected by Breast Cancer should be given to the patient. Patients should be informed that clinically significant germline variants in breast cancer genes are a cause of cancer and knowing whether a germline variant is involved in causing their cancer can be helpful for their current and future management. The clinician may like to describe the specific relevance of the test for the specific patient. The patient should also be aware that the result can provide information of relevance to the wider family. However, it is important to remember that most tests are normal and therefore detailed discussions regarding risk management for patient and relatives, prior to testing, are not required.

The Genetic Test Request Form includes a list of discussion points to cover pre-test thereby providing an aid memoire for clinicians.

What are the insurance implications for cancer patients?

If a cancer patient applies for life cover, critical illness or income protection cover after the gene test is performed, then it will need to be disclosed, along with the other information about their

cancer diagnosis. This is unlikely to have impact on the cover/terms they are offered over and above the impact of their cancer diagnosis.

If the gene test was performed after an insurance policy was set-up the result does NOT need to be disclosed to that insurer.

Are there insurance implications for the cancer patient's relatives?

Relatives would need to tell the insurance company about the cancer diagnosis in the family and if a clinically significant gene variant has been found when asked about their family history (if they are aware of it). If the genetic test result is normal some insurance companies may take this into consideration to mitigate the unfavourable impact of the family history on the policy.

Unaffected individuals do not have to disclose their personal results of predictive gene testing to insurance companies but may choose to do so, particularly if they have not inherited the clinically significant variant known to be present in the family.

Which consent and lab form should I use?

For patients with breast cancer, there is a specific Genetic Test Request Form which is different from the standard genetic testing form for NHS Lothian. This combines the consent form, test criteria and request form for ease of use. Once completed, a copy of the request can be scanned to the TrakCare record or a note put in the patient electronic records to show that the genetic test has been requested. The request sheet should be sent with the patient's labelled blood sample (1 x 3ml EDTA) to the Molecular Genetics Lab, South East Scotland Genetic Service, Western General Hospital, Crewe Road, Edinburgh, EH4 2XU.

How long does it take to get a result?

The results of full analysis typically take about 8-10 weeks. However, it may take 4 weeks if 'urgent' testing is requested due to immediate management decisions. For more information see FAQ section 'When should discussion of testing be undertaken?'

IF THERE IS A KNOWN CLINICALLY SIGNIFICANT VARIANT IN THE FAMILY, PLEASE TAKE THE SAMPLE, BUT ALSO REFER TO CLINICAL GENETICS. The result takes 2-4 weeks.

What genes will be analysed / tested?

The current genes tested on the germline breast cancer panel are BRCA1, BRCA2, TP53, PTEN, STK11, PALB2, ATM, CHEK2, RAD51C and RAD51D. In the future, testing for additional genes related to cancer *may* become available in some cases. However, this is not likely within the next 5 years.

If the patient has had multiple other cancers or if there is family history that you are concerned about, the patient can be referred to the Clinical Genetic Service.

What if a patient meets the criteria but chooses not to have a test?

The test is optional. A patient may decline to be tested, ask to have longer to think about testing or be referred to Clinical Genetics if they want, or need, more detailed discussions. If the patient

does not wish to have testing but would like to put a DNA sample into storage in case this is useful for their relatives in the future, please make this VERY clear on the Genetic Test Request Form.

What if a patient does not meet the testing criteria but wants a test?

Patients who do not meet the genetic testing criteria may be eligible for a test on account of their family history (Manchester or CanRisk Score). Queries about whether patients are eligible should be directed by email to WGH.ClinicalGenetics@nhslothian.scot.nhs.uk . Alternatively, they could choose to have the test privately by a private company.

What if my patient or a member of their family has already had genetic testing?

If a member of the family has already had a test for genes associated with cancer predisposition, please contact the Genetics unit by email on: WGH.ClinicalGenetics@nhslothian.scot.nhs.uk and note this (preferably including the relative's name and date of birth) on the lab form. It may influence the testing that is performed. If the patient themselves has previously had genetic testing, the Clinical Genetics Service will need to verify if this testing was undertaken to the same standard as current testing. If not, the testing may need to be repeated.

Who will give the patient the result of the test?

All mainstreamed lab reports will be sent to the Cancer Clinician involved in the mainstreaming. This is why it is essential that they write their email address written legibly on the combined Consent Laboratory Request. It is the **Cancer Clinician's responsibility to ensure that the lab report is uploaded to the patient electronic record.**

For **normal results, the Cancer Clinician** involved in mainstreaming and NOT Clinical Genetics will **inform patients** (see below).

What happens if no gene variant is identified*?*

The Cancer Clinician involved in mainstreaming should inform the patient. A suggested result letter and Patient Information Leaflet can be found at Appendix 4.3. A copy result letter can be sent to the GP and if appropriate also to any other Breast Care Team involved (Oncologist and/or Breast Surgeon). It should be uploaded to the patient electronic record.

There is also a Patient Information Leaflet that you may find helpful to provide to the patient in Appendix 4.3. If the patient has additional questions about the result, they can be referred to the Clinical Genetics team.

Please note, patients and their relatives may still be eligible for enhanced mammographic surveillance on account of their family history. Relatives can seek advice about enhanced screening via their GP.

What happens if a clinically significant gene variant is identified?

The Cancer Clinician involved in mainstreaming will receive a copy of the lab report and can inform the patient. The Cancer team should use the information as appropriate for their cancer management.

The Clinical Genetics service will also receive the lab report and will write directly to the patient informing them of the result, copying in the Breast Care Team (Oncologist and/or Breast Surgeon)

and GP. This letter will also be uploaded to SCI Store/ Trak if the patient is registered for NHS Lothian Trakcare. The patient will be sent an appointment soon to attend Clinical Genetics to discuss their result. The Genetic team will discuss the test result, the implications for relatives, and the process for how their relatives can access genetic testing.

What happens if there is a variant of unknown clinical significance (VUS) is identified that needs further assessment?

Very occasionally (<1%), the lab identifies a variant that does not fulfil the criteria for pathogenic status, where further evaluation might be possible. The variant does not have enough evidence to state whether it increases the risk of cancer or is benign (harmless). Guidelines recommend that a 'VUS' is not used to guide a patient's cancer management. It does not give information about cancer risks. Future technological developments are required to clarify the situation.

In such cases, both the Cancer Clinician involved in mainstreaming, and the Clinical Genetic service will be sent the lab result. The Cancer Clinician is encouraged to speak with the genetic service.

The Clinical Genetic service will write directly to the patient to inform them of the result and offer an appointment soon to review the family history and provide the patient with the opportunity to discuss any questions. A copy result letter will be sent to the Breast Care Team (Oncologist and/or Breast Surgeon) and GP and it will be uploaded to SCI Store/ Trak if the patient is registered for NHS Lothian TrakCare. **It is often not possible to clarify further if the variant is of clinical significance.** The family history will be used to consider whether any additional cancer screening is suggested to individuals in the family.

Variants may be re-classified over time, which may be useful for the patient, and their relatives. Patients who attend the Clinical Genetics service would be encouraged to check with the genetic service every 5 years to ask if there has been a change in the classification of the variant.

What if there is an equivocal result?

No equivocal reports are issued. The Molecular Genetics laboratory reviews all results, determines the pathogenicity of any identified sequence variants, and interprets their clinical relevance. We have a sophisticated clinical and bioinformatic interpretative system that allows us to do this. The reports thus include clear information about whether a clinically significant variant was identified. Very occasionally (<1%), there are sequence variants that do not fulfil the criteria for clinically significant variants, but merit further assessment (see above).

What if the test fails?

Very occasionally, testing fails as the laboratory are not able to extract suitable DNA from the patient's sample. This is more likely to happen in a patient undergoing chemotherapy. In this case, the laboratory will request a repeat sample.

What if new evidence in the future shows a variant is pathogenic?

If further information becomes available and any variants are reclassified, the genetics laboratory may re-issue reports. It is important to remember that rare sequence variants in these genes are

collectively common in the general population (present in about 10%), and the great majority are not pathogenic.

If a clinically significant variant is identified who will follow-up the patient's relatives?

If the patient attends their appointment with the Clinical Genetic Service, they will be provided with "To whom it may concern" letters to give to relatives. The letter will explain that a cancer predisposition gene variant has been identified in the family and that relatives can ask their GP to refer them to their local genetics service to discuss the implications. Genetic Services will NOT approach family members directly. This is standard practice in Clinical Genetics.

If the patient does not have a clinically significant variant, are there additional genetic tests that should be performed?

Some patients may be eligible for further tests, particularly if they have multiple primary cancers or if there is an extensive family history of cancer. We recommend that such patients are referred to Clinical Genetics.

Who should I contact if I have any questions or suggestions?

These should be addressed to WGH.ClinicalGenetics@nhslothian.scot.nhs.uk. We get many referrals and enquiries to the service about hereditary cancer. It would be helpful to identify when emailing if your question or comment relates to Germline Breast Cancer Genetic Testing.

If there is anything that you would like further clarity about, please contact: WGH.ClinicalGenetics@nhslothian.scot.nhs.uk

4. APPENDICES

4.1– Pre-test patient information leaflet - EXAMPLE

NHS Lothian

GENETIC TESTING FOR PEOPLE AFFECTED BY BREAST CANCER

WHY HAVE I BEEN OFFERED A GENETIC TEST?

Around one in eight women and a small number of men will be diagnosed with breast cancer during their lives. Some of these are eligible for genetic testing.

Only a small number of those tested will have changes in their genetic makeup that has affected their risk of getting cancer. This information may help your doctor and you in **making the best choices for your current and future treatments**.

It is important for you to know that the test can also give you information about your risk of developing other cancers. The results might also provide information about **your relatives'** risk of developing cancer.

THE TEST

The test is carried out on a blood sample and looks for changes in genes* known to be associated with breast cancer risk.

THE RESULTS

Possible outcomes of genetic testing:

- **No gene change identified:** In most people the test will NOT find a gene change. This reduces the chance of a predisposing gene being responsible for your cancer.
- **"Pathogenic" or "Likely Pathogenic" (disease-causing) gene change identified**: This confirms an inherited risk and may help in making decisions about your treatment. It may also confirm that your risk of another cancer is increased. Because we share genes with our relatives, there is a chance they may have an increased risk of cancer too. It would be possible for them to have a genetic test.
- **"Variant of unknown clinical significance":** We all carry variations in our genetic code. The majority of these are NOT linked to disease. If testing identifies a variant which requires further assessment, this will be discussed with you.

WHAT WILL HAPPEN NEXT IF I AGREE TO TESTING?

If you decide to have the test, you will be asked to sign a consent form. A blood sample will be taken for the test and sent to the laboratory.

WHAT IF I WANT MORE INFORMATION ABOUT HAVING THE TEST?

Genetic testing is now an **important test in cancer care** and can provide your specialist with information to help decide the best treatment for your cancer. Knowing about

increased risk means that additional screening to detect the early signs of cancer may be available, or there may be other steps to reduce the risk.

It can also provide **important information for your relatives**, which may reduce their chance of developing a cancer in the future.

However, you do have the right not to have genetic testing. Please speak with your cancer clinician if you have questions. Alternatively, you can contact the duty genetic counsellor (contact details below).

HOW WILL I RECEIVE MY RESULT?

Your cancer clinician will inform you of the result. The result will usually take up to 10 weeks but may be sooner if your doctor requests this for immediate clinical reasons (not usually before 4-5 weeks).

If your test finds a change in one of the genes, the genetic clinic will send you an appointment soon afterwards. At the genetic clinic you will meet with a genetic clinician who will discuss your result with you and what it might mean for you and your relatives. There will be time to think about the best way forward for you and they can spend time answering any questions you might have. If appropriate, they will also provide you with information that you can share with relatives.

WHAT IF I STILL HAVE MORE QUESTIONS?

If your genetic test does not find any genetic changes but you have a family history of cancer, it is still possible that your relatives may have an increased risk of developing cancer. If you are concerned about your family history, you can ask your GP or cancer clinician to refer you to Clinical Genetics.

A limitation of any genetic test is that just like much of medical science, we cannot yet know with certainty all the factors that influence health. Very occasionally the current understanding of a gene change or variant may change as more information becomes available.

*Current breast cancer panel: *BRCA1, BRCA2, PALB2, PTEN, TP53, STK11, CHEK2, ATM, RAD51C, RAD51D.*

CONTACT DETAILS FOR THE GENETIC SERVICES

Duty Genetic Counsellor
South East of Scotland Clinical Genetics Service, Institute of Genetics and Cancer
Western General Hospital
Crewe Road South
Edinburgh, EH4 2XU
Tel: 0131 537 1116 Email: WGH.clinicalgenetics@nhslothian.scot.nhs.uk

4.2 Appendix 2 – Lab request form - EXAMPLE

Please complete using BLACK ink- form will be scanned in lab
For office use only - EBU

NHS Lothian
Lothian University Hospitals Division

Breast Panel Genetic test request form (Affected patients)

South East Scotland Genetic Service

Western General Hospital, Edinburgh, EH4 2XU
Clinical Genetics (*clinical enquiries only*) Email: WGH.ClinicalGenetics@nhslothian.scot.nhs.uk Tel: 0131 537 1116
Molecular Genetics (DNA) Lab Email: edinburgh.dna@nhslothian.scot.nhs.uk Tel: 0131 537 1116/1270

PATIENT DETAILS (printed label) Sex M /F Required: Name, date of birth, CHI or 1st line of home address and postcode	**CLINICAL DETAILS** Breast Cancer (BC) at age:..... **Please tick all that apply** ☐ BC <40 years ☐ Bilateral BC, both <60 years ☐ Triple-negative BC <60 years ☐ BC + Ovarian Cancer, any age ☐ BC & 1 First Degree Relative with BC, both <45 yrs ☐ Male BC, any age ☐ Manchester score ≥15
Clinician email for report (ESSENTIAL): **Clinician Name (CAPITALS):** **Department:** **Hospital:**	**Any relevant family history:**
Please note: Patients can be referred to Clinical Genetics for assessment e.g. if an individual does not fit the criteria for mainstream testing, but has a family history or has questions. Genetic testing of unaffected individuals will not be undertaken.	

DISCUSSION

1. ***Implications for self*** The result of my test may indicate that I have an increased risk of developing a further breast cancer and possibly an increased risk of other types of cancer. The result may be helpful in planning current cancer treatment and the management of future cancer risk.
2. ***Family implications*** The results of my test may have implications for other members of my family. I acknowledge that my results may sometimes be used to inform the appropriate health care of others. This could be done in discussion with me, or in such a way that I am not personally identified in this process.
3. ***Uncertainty*** The results of my test *may* reveal genetic variation whose significance is not yet known. Deciding whether such variation is significant may require sharing of information about me including (inter)national comparisons with variation in others. I acknowledge that interpretation of my results may change over time as such evidence is gathered.
4. ***DNA storage*** Normal laboratory practice is to store the DNA extracted from my sample even after the current testing is complete. My sample might be used as a 'quality control' for other testing, for example, that of family members.
5. ***Data storage*** Data from my genetic test will be stored to allow for possible future interpretations.
6. ***Health records*** Results from my genetic test and my test report will be part of my Patient Health Record.

PATIENT CONSENT

I consent to my sample being tested and have been given the information leaflet on genetic testing

Patient Signature: ..... **Date:** .....

SAMPLE DETAILS
Required: Blood in Potassium EDTA (KE) tube (1x 3ml)

Taken by: Name (print) Signature:

Date taken: Time taken: High risk (*see over*) Y / N

☐ URGENT *(Results are normally reported in 8-10 weeks. If the results are required for treatment purposes in the next 4-8 weeks please mark as urgent)*
Please send result to Clinician named above and to Edinburgh.DNA@nhslothian.scot.nhs.uk
Please ALSO send Class 3,4,5 variants to WGH.clinicalgenetics@nhslothian.scot.nhs.uk.

4.3 –- Result no gene variant identified.

Suggested letter &/or Patient Information Leaflet that Cancer service could provide to patient - EXAMPLE

Dear Patient

You will remember that you provided a blood sample so that the genetic laboratory could look for changes in the genes known to be associated with breast cancer predisposition (BRCA1, BRCA2, PALB2, PTEN, STK11, TP53, ATM, CHEK2, RAD51C and RAD51D).

We now have the result of the analysis of these genes and the laboratory has **not** found any disease-causing changes.

The probability that a high-risk gene is the explanation for your cancer development has been reduced.

Very occasionally the current understanding of a gene variant may change as more information becomes available.

An information sheet is enclosed, providing further details about your results.

With best wishes

Yours sincerely

Breast Health Professional

Enclosure: Receiving a Normal Breast Gene Panel Result

c.c. GP
Breast surgeon
Oncologist

RECEIVING A NORMAL BREAST GENE PANEL TEST RESULT

Patient label

You had a breast gene panel test because you have had cancer.

The test result is normal. No disease-causing gene variants were identified in your blood sample.

The following genes were tested: BRCA1, BRCA2, PALB2, PTEN, STK11, TP53, ATM, CHEK2, RAD51C, RAD51D. Very occasionally the current understanding of gene variants may change as more information becomes available.

WHAT DOES THIS RESULT MEAN FOR ME?

This means we have not found a gene variant which would put you at high risk of developing another new cancer.

A normal result is common. Most people with breast cancer receive this result. If you have a strong family history of breast, ovarian or stomach cancer, or if you developed cancer at an unusually young age, it may be helpful to look into things further. You can ask for a referral to the Clinical Genetics Service if you have questions or concerns about this.

Very occasionally variants in other genes can be involved in causing breast cancer. Also new discoveries are being made all the time. Your sample is stored in case further gene testing is requested in the future.

WHAT DOES THIS RESULT MEAN FOR MY RELATIVES?

This result is good news for your relatives, as it means they are unlikely to be at high increased risk of developing breast cancer themselves. You may wish to share this result with them.

If you have had a different cancer previously, or if you have a family history of cancer, it is still possible that your relatives may have an increased risk of developing cancer. If you think that this applies to you, you can talk to your GP or hospital clinician.

Anyone registered female with a GP will be invited for NHS mammograms from 50 and 71 years as part of the National Breast Screening Program. Depending on the family history, some people may be eligible for mammograms starting from 35 or 40 years, even if there has been a normal breast gene panel test in the family. For example, if you developed breast cancer under 40 your daughters would be eligible for early access. If your relatives wish to discuss their own risks of cancer, they can speak with their GP.

If you have any questions, please contact the Edinburgh Clinical Genetics Service on 0131 537 1116 or email on WGH.clinicalgenetics@nhslothian.scot.nhs.uk