Liverpool Women's
NHS Foundation Trust

The test result

Overview: Receiving & giving the test result

1) Reading the genetic test report
2) Possible test results
3) Giving the result
4) Possible implications of result for the patient and their wider family

Reading the genetic test report

NW Genomic Laboratory Hub (Manchester Site)
Manchester Centre for Genomic Medicine
6th Floor, St Mary's Hospital, Manchester M13 9WL
Scientific Operational Director: Dr E. Howard
www.mangen.org.uk mft.genomics@nhs.net Tel +44(0) 161 276 6122

NHS North West
NHS Genomic Laboratory Hub

Eleanor Taylor
Trainee Genetic Counsellor
North West Coast NHS Genomic Medicine Centre - Liverpool
Liverpool Women's NHS Foundation Trust,
Crown Street,
Liverpool
L8 7SS

INHERITED CANCER PANEL GENETIC TESTING REPORT
INHERITED BREAST & OVARIAN CANCER SUBPANEL

NAME:
DATE OF BIRTH:
SEX:
NHS No:
POSTCODE:
YOUR REF:
OUR REF: 21006706.421
DATE: 4-May-2021

REASON FOR REFERRAL: This patient has been diagnosed with breast cancer. Screening of a panel of genes associated with inherited predisposition to breast and ovarian cancer has been requested.

THIS PATIENT'S REPORT HAS BEEN UPDATED DUE TO CORRECT THE HOSPITAL NUMBER. PLEASE ENSURE THAT ALL COPIES THE ORIGINAL REPORT (ISSUED 27-Apr-2021) ARE CLEARLY MARKED AS NO LONGER VALID AND CROSS REFERENCED TO THIS REPORT SO THAT THERE IS A CLEAR AUDIT TRAIL.

RESULTS:

NAME (DoB)	RESULT	INTERPRETATION
	NO PATHOGENIC VARIANT IDENTIFIED	GENETIC CAUSE NOT IDENTIFIED

KEY: * Variant classification has been performed according to ACGS guidelines[1].

COMMENTS: This patient's lymphocyte DNA sample was screened for variants in a virtual subpanel of genes associated with inherited breast and ovarian cancer (see notes).

No variants of clinical relevance, including whole exon copy number changes, were detected in the panel of genes analysed.

In conclusion, we have been unable to identify a genetic cause for this patient's clinical presentation.

NOTES:
Please see page 2 for technical details of the analysis and references.

PREPARED & AUTHORISED:

Philip Smith
Clinical Scientist

CHECKED:

Clinical Scientist

Reading the genetic test report

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Contact details of the testing laboratory

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PREPARED & AUTHORISED:
Philip Smith
Clinical Scientist

CHECKED:
Clinical Scientist

Reading the genetic test report

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Trainee Genetic Counsellor
North West Coast NHS Genomic Medicine Centre
Liverpool Women's NHS Foundation Trust,
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Details of the clinician who has ordered the test

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NOTES:
Please see page 2 for technical details of the analysis and references.

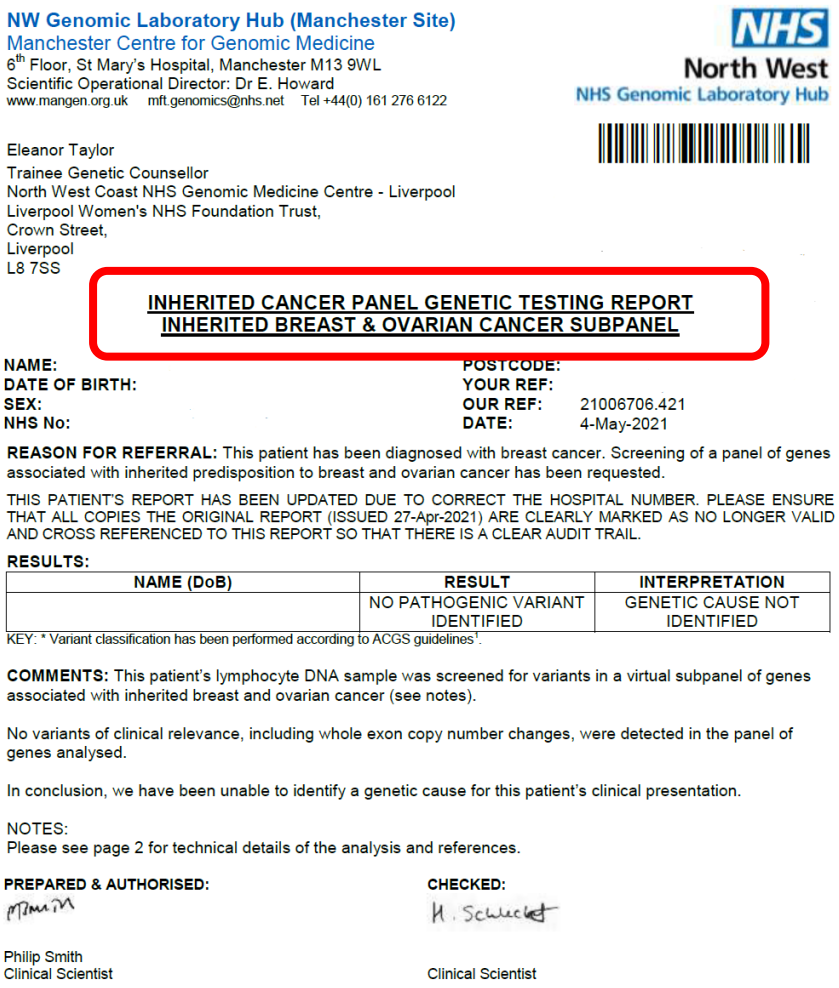
PREPARED & AUTHORISED:
Philip Smith
Clinical Scientist

CHECKED:
Clinical Scientist

Reading the genetic test report

INHERITED CANCER PANEL GENETIC TESTING REPORT
INHERITED BREAST & OVARIAN CANCER SUBPANEL

Summary of the test that was performed



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COMMENTS: This patient's lymphocyte DNA sample was screened for variants in a virtual subpanel of genes associated with inherited breast and ovarian cancer (see notes).

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NOTES:
Please see page 2 for technical details of the analysis and references.

PREPARED & AUTHORISED:
Philip Smith
Clinical Scientist

CHECKED:
Clinical Scientist

Reading the genetic test report

NAME:
DATE OF BIRTH:
SEX:
NHS No:
POSTCODE:
YOUR REF:
OUR REF: 21006706.421
DATE: 4-May-2021

Summary of patient demographics and unique laboratory number

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SEX:		**OUR REF:**	21006706.421
NHS No:		**DATE:**	4-May-2021

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NOTES:
Please see page 2 for technical details of the analysis and references.

PREPARED & AUTHORISED:
Philip Smith
Clinical Scientist

CHECKED:
H. Schlecht
Clinical Scientist

Reading the genetic test report

All re-issued reports will request that the original reports are marked as
'NO LONGER VALID'

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PREPARED & AUTHORISED:
Philip Smith
Clinical Scientist

CHECKED:
Clinical Scientist

Reading the genetic test report

Summary of the reason for referral

REASON FOR REFERRAL:

- The patient has been diagnosed with breast cancer.
- Screening of a panel of genes associated with an inherited predisposition to breast and ovarian cancer has been requested

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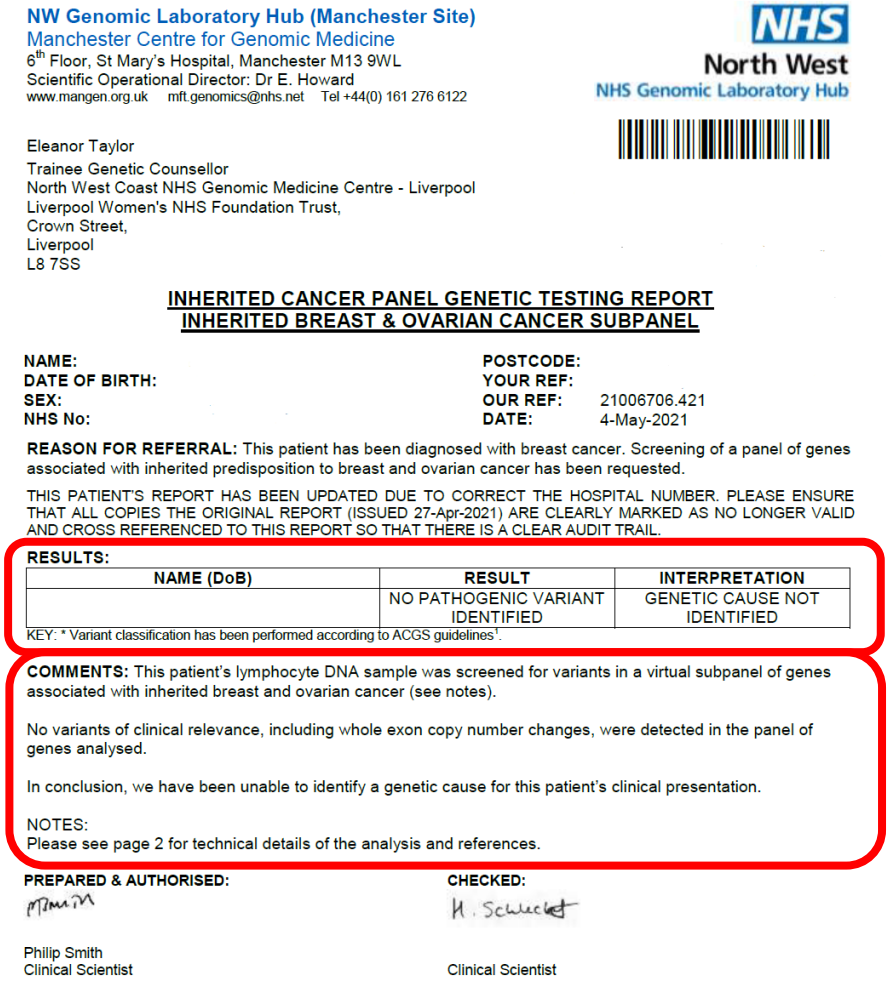
Clinical Scientist

CHECKED:
H. Schlecht
Clinical Scientist

Reading the genetic test report

The main body of the test report will contain:

1) A clear statement of the test result
2) Interpretive comments



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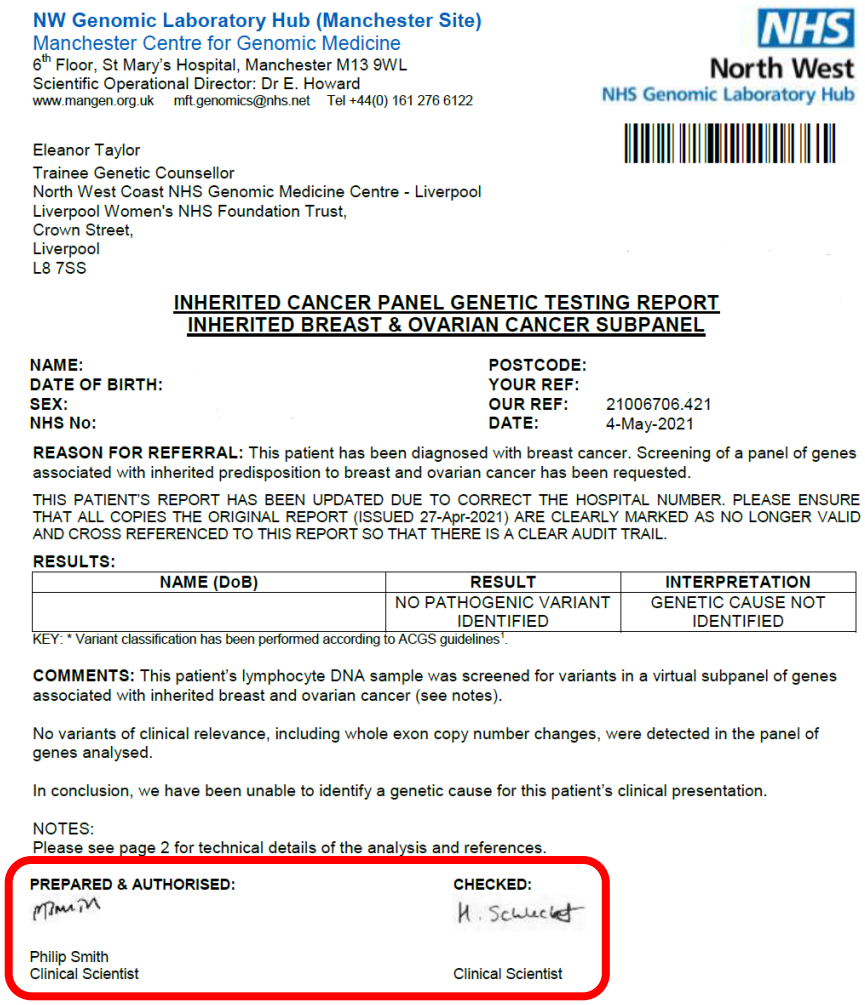
PREPARED & AUTHORISED:
Philip Smith
Clinical Scientist

CHECKED:
Clinical Scientist

Reading the genetic test report

The test report will have been checked for accuracy by two scientists prior to release



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No variants of clinical relevance, including whole exon copy number changes, were detected in the panel of genes analysed.

In conclusion, we have been unable to identify a genetic cause for this patient's clinical presentation.

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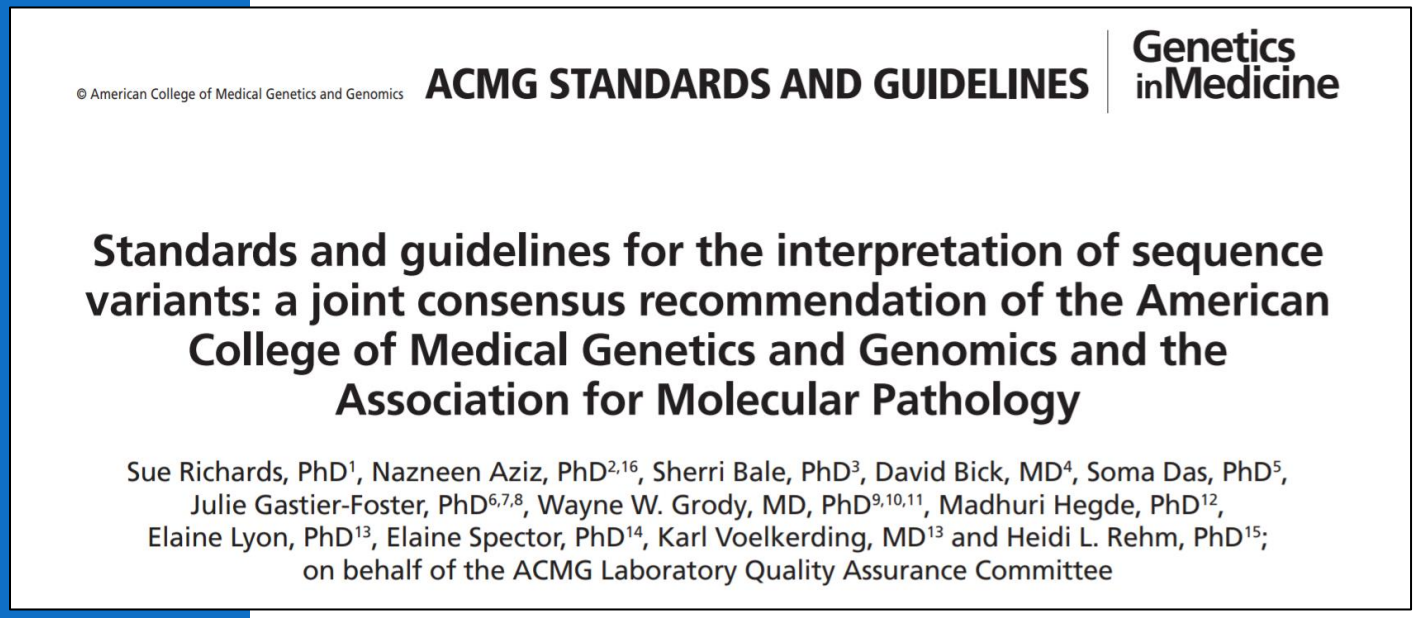
PREPARED & AUTHORISED:
Philip Smith
Clinical Scientist

CHECKED:
Clinical Scientist

Possible genetic test results

All variants identified during the genetic testing process are analysed using the guidelines published by the American College of Molecular Genetics and Genomics (ACGM)



ACMG STANDARDS AND GUIDELINES | Genetics inMedicine

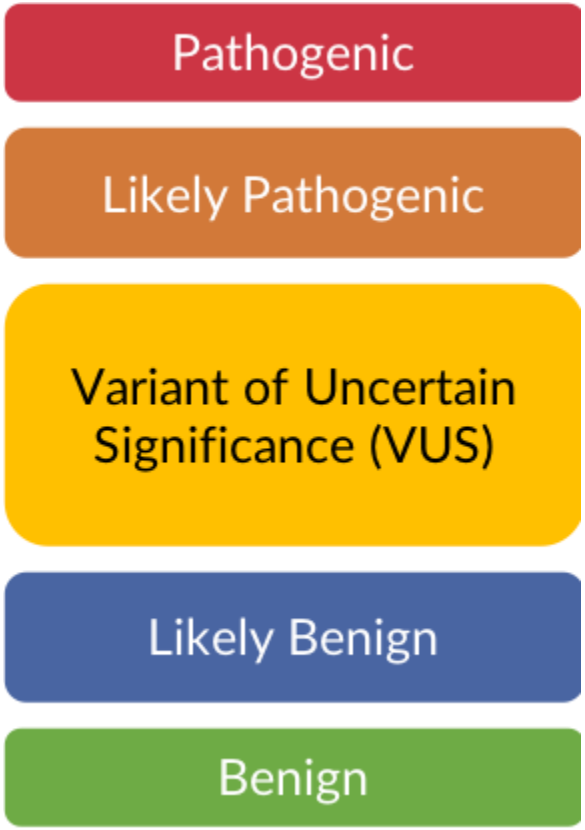
Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

Sue Richards, PhD[1], Nazneen Aziz, PhD[2,16], Sherri Bale, PhD[3], David Bick, MD[4], Soma Das, PhD[5], Julie Gastier-Foster, PhD[6,7,8], Wayne W. Grody, MD, PhD[9,10,11], Madhuri Hegde, PhD[12], Elaine Lyon, PhD[13], Elaine Spector, PhD[14], Karl Voelkerding, MD[13] and Heidi L. Rehm, PhD[15]; on behalf of the ACMG Laboratory Quality Assurance Committee

Link to paper: https://doi.org/10.1038/gim.2015.30

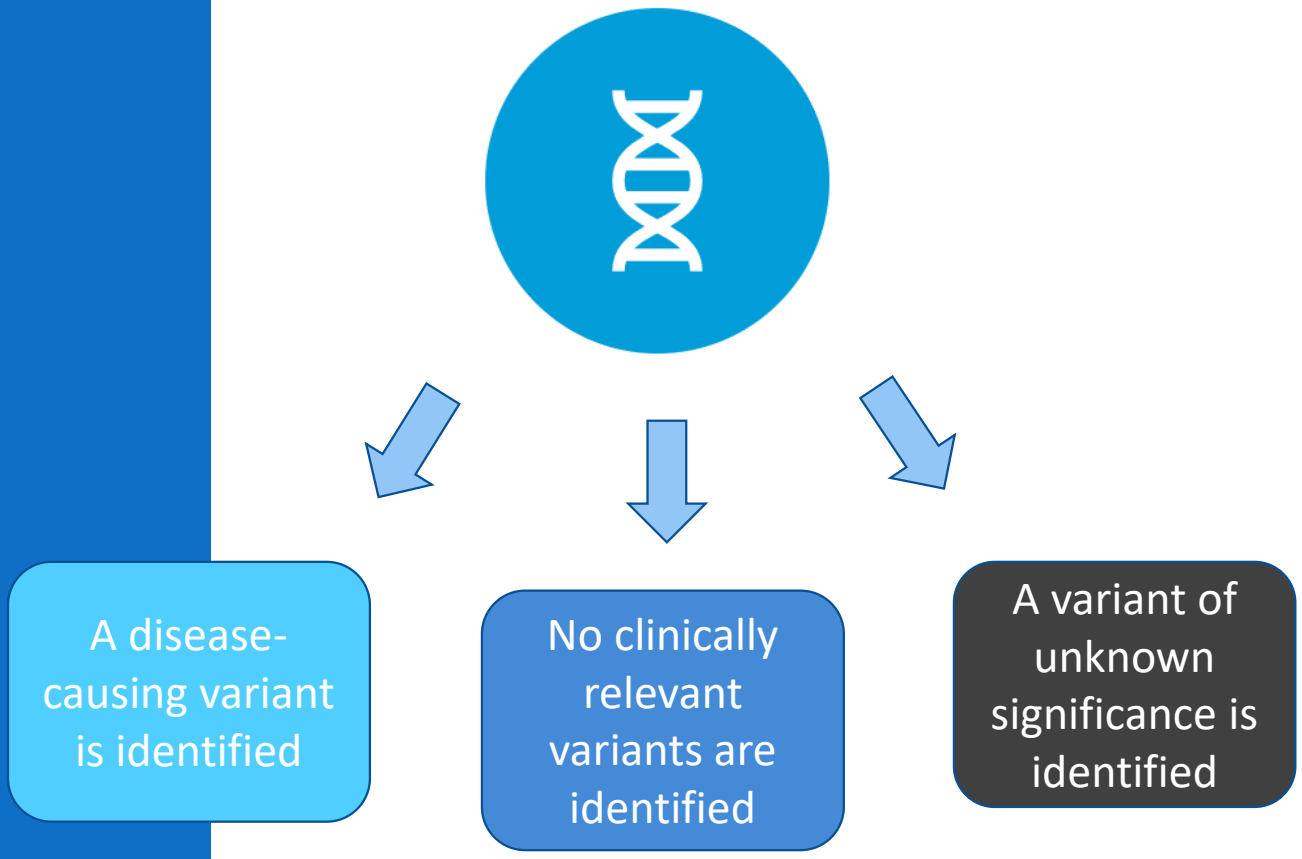
Possible genetic test results

All identified variants are assigned to one of five categories:



Possible genetic test results

There are three potential outcomes of the genetic testing process:



1) A disease-causing variant

The identification of a pathogenic or a likely pathogenic variant in a BRCA/PALB2 gene indicates that there is an inherited genetic cause of the patient's breast cancer:

RESULTS:

NAME (DoB)	RESULT	CLASSIFICATION*	INTERPRETATION
	BRCA1 c.5266dupC p.(Gln1756ProfsTer74) HETEROZYGOUS	Pathogenic	Confirms a clinical diagnosis

KEY: * Variant classification has been performed according to ACGS guidelines[1].

COMMENTS: This patient's lymphocyte DNA sample was screened for pathogenic variants in the BRCA1, BRCA2 and PALB2 genes using DNA sequence analysis and copy number analysis.

A heterozygous BRCA1 c.5266dupC p.(Gln1756ProfsTer74) variant was identified in this patient's lymphocyte DNA sample. No other clinically relevant variants were identified in this patient.

The BRCA1 c.5266dupC p.(Gln1756ProfsTer74)variant has been classified as pathogenic[1].

This patient should be referred to their local clinical genetics centre for genetic counselling and to arrange testing for this pathogenic variant for other at risk family members, as appropriate.

In conclusion, we have identified a pathogenic BRCA1 c.5266dupC p.(Gln1756ProfsTer74) variant, which confirms a diagnosis of hereditary breast and/or ovarian cancer in this patient. Please refer to current NICE guidance regarding access to PARP inhibition therapy. In addition, this patient remains at risk of developing further BRCA1 related cancers.

2) An uninformative result

Tests which only identify benign/likely benign variants, or no variants at all, are classified as being uninformative, rather than 'negative', as there may still be a genetic cause to the patient's cancer:

- There may be an alteration that has not been identified due to the limitations of the current laboratory technology.
- There may be an alteration in a different gene which hasn't been tested.

RESULTS:

NAME (DoB)	RESULT	INTERPRETATION
	NO PATHOGENIC VARIANT IDENTIFIED	GENETIC CAUSE NOT IDENTIFIED

KEY: * Variant classification has been performed according to ACGS guidelines[1].

COMMENTS: This patient's lymphocyte DNA sample was screened for pathogenic variants in the BRCA1, BRCA2 and PALB2 genes using DNA sequence analysis and copy number analysis.

No variants of clinical relevance, including whole exon copy number changes, were detected in the panel of genes analysed.

These results do not exclude the possibility that this patient may have a pathogenic variant in another cancer susceptibility gene. If there is a family history of breast/ovarian cancer this patient should be referred to their local clinical genetics centre, as appropriate.

In conclusion, no pathogenic BRCA1, BRCA2 or PALB2 variant was identified.

2) A variant of unknown significance

In some cases, there is not enough evidence available to classify a variant as pathogenic/likely pathogenic or benign/likely benign. These variants are known as variants of unknown significance a VUS.

RESULTS:

NAME (DoB)	RESULT	INTERPRETATION
	NO PATHOGENIC VARIANT IDENTIFIED (see comments)	GENETIC CAUSE NOT IDENTIFIED

KEY: * Variant classification has been performed according to ACGS guidelines[1].

COMMENTS: This patient's lymphocyte DNA sample was screened for pathogenic variants in the BRCA1, BRCA2 and PALB2 genes using DNA sequence analysis and copy number analysis.

No variants of clinical relevance, including whole exon copy number changes, were detected in the panel of genes analysed.
During analysis we did identify a heterozygous variant of unknown clinical significance BRCA1 c.5332+3A>G. Review of the available evidence did not meet criteria for classification as likely pathogenic.

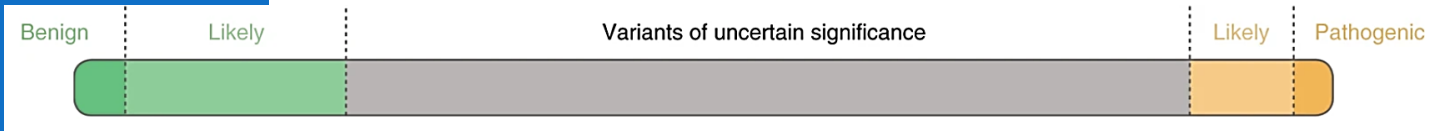
These results do not exclude the possibility that this patient may have a pathogenic variant in another cancer susceptibility gene. If there is a family history of breast/ovarian cancer this patient should be referred to their local clinical genetics centre, as appropriate.

In conclusion, no pathogenic BRCA1, BRCA2 or PALB2 variant was identified.

2) A variant of unknown significance

A VUS is an alteration in the gene sequence with **unknown** consequences in terms of the function of the gene product and the risk of disease.

A VUS can fall anywhere along the spectrum of being close to 'likely benign' to being close to 'likely pathogenic':



As a result, **only variants that are classified as pathogenic/likely pathogenic should be used to direct clinical management.**

This also means predictive genetic testing cannot be offered to the patient's wider family.

All variants of unknown significance will be kept under review by the laboratory team. The laboratory will automatically be notified if the classification of a variant has changed to 'likely pathogenic' or 'pathogenic' and they will issue a new genetic test report for any patient in their database who carries this re-classified variant. The clinician who receives the new genetic test report will be responsible for sharing this information with the patient.

Check the small print…..

The ‘notes’ section on the laboratory report contains details of what testing was performed, what genes were examined, the quality parameters of the test and the limitations of the test:

NOTES: *A panel of 115 cancer genes have been targeted using Agilent SureSelect Custom Design and sequenced on the NextSeq 500 (Illumina), according to the manufacturer's protocols.*

Method: Enrichment was performed with a custom design Sure Select custom target enrichment kit (Agilent) for the NextSeq (Illumina) system. The target enrichment design consists of the coding region of transcripts, including the immediate splice sites (+/-15 bases), for genes detailed below. The samples were sequenced using a NextSeq (Illumina), according to the manufacturer's protocols. Sequence data was aligned to hg19 human genome using BWA-MEM v0.6.2 and abra v0.96. Variant calling was by a custom bioinformatic analysis pipeline (version v2.1.0) validated to detect SNVs and small insertion/deletion variants (<40bp) to 5% variant allele fraction (VAF) Reported sequence changes retested via Sanger sequencing using BigDye v3.1. Copy number analysis using MLPA MRC-Holland probe mixes to identify whole exon deletions and duplications: P002-D1 (BRCA1) and P045-D1 (BRCA2 [includes an assay to include CHEK2 c.1100delC and CHEK2 exons 1 and 9]) and P260-C1 (PALB2). Exons are numbered systematically for each probe mix.
Known polymorphic variants were subsequently filtered out of the data obtained using bioinformatic analysis. Variant nomenclature follows HGVS guidelines (https://varnomen.hgvs.org/) with nucleotide 1 counted as the first nucleotide of translation initiation codon using Genbank accession numbers listed above and therefore nomenclature and exon numbering may differ from that given in the quoted literature.

Quality: >99.9% of the target coding region of a total 115 gene enrichment was covered to a minimum depth of 100x with an average read depth of 1934x.

PANEL TESTED: A complete list of the virtual panel of genes analysed in this patient and respective GenBank accession numbers is listed below.

R208: BrOv Inherited breast cancer and ovarian cancer (3)
BRCA1 (NM_007294.3), BRCA2 (NM_000059.3), PALB2 (NM_024675.3),

A minimum coverage depth of 100x is required for optimum detection of heterozygous single nucleotide variants. Any genes with less than 90% coverage at a read depth of 100x are listed below.

NONE

Heterozygous variants assessed and not currently considered to be clinically relevant:

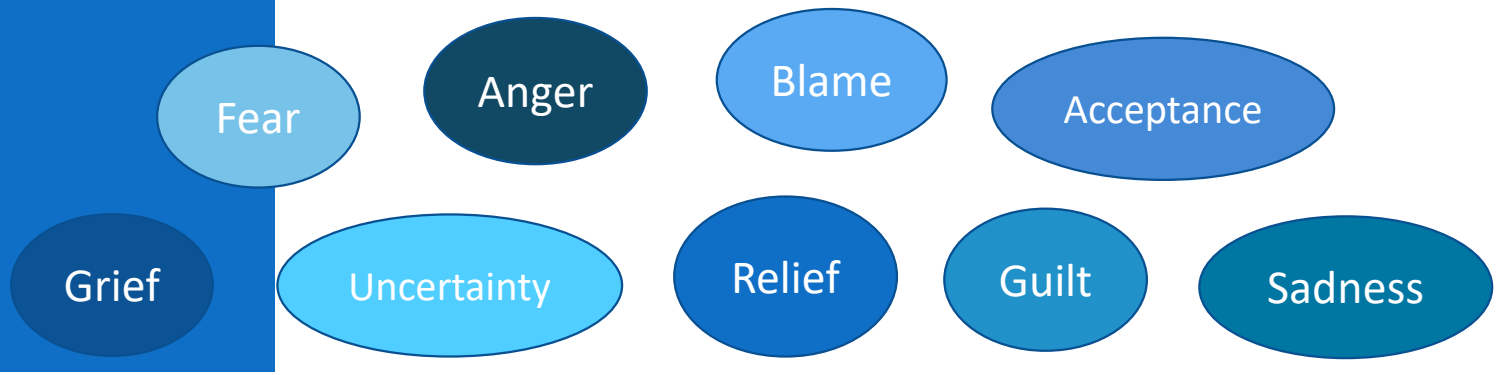
BRCA1 c.5332+3A>G

REFS: (1) ACGS Best Practice Guidelines for Variant Classification 2020. https://www.acgs.uk.com/quality/best-practice-guidelines/.

Giving the test result

Practical considerations when giving the genetic test result:

- Check the test report prior to the results appointment;
- Consider having the report checked/witnessed by a 2nd clinician;
- Disclose the result at the start of the appointment;
- Confirm the name and date of birth of patient and cross-check details against the genetic test report, before disclosing the result;
- State the result in simple terms i.e. leave no room for ambiguity;
- Recognise that the result can provoke a range of emotions and meet the patient with empathy



Responsibilities of the clinician

The clinician giving the test result will need to explain what the result means for the patient

e.g. will the result change their treatment recommendations?

All patients who are found to have a pathogenic gene alteration should be referred to their local Genomic Medicine Service for a full implications discussion:

- Does the result change their cancer risk?
- What surveillance options are available to them?
- What risk reducing strategies are available to them?
- What are their reproductive options?
- What support groups are available to them?
- Are they eligible for any research trials?
- What does this mean for their family members?

If you have any questions about the genetic testing process or the interpretation of the genetic test result, please contact:

The North West Genomics Laboratory Hub on

mft.genomics@nhs.net

or

The Genetic Counselling team at the Liverpool Centre for Genomic Medicine on

lwft.clingen@nhs.net