

***Trust Logo***

**<GLH region name>**

**NHS Genomic Laboratory Hub**

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| ***Head of Department***  *Name* |  | *Local Genetics Service*  *Local Trust*  *Address*  *Address*  *Post Code*  *Web site address* |
| General Enquiries: *telephone contact*  Email: *generic email address* |
|  | | |

**GENOMIC LABORATORY REPORT**

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| --- | --- | --- |
| Dr xxx | **Patient Name:** | **Jane DOE** |
| Consultant | Gender: | Female |
| <<Hospital address>> | Date of Birth: | 14 Jan 1968 |
| NHS No: | 123 456 7890 |
| Hospital No: | NK |
| Your ref: | GC12345 |

**Reason for testing**

Diagnostic testing. <<Referral reason>>. Patient phenotype / HPO terms

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| --- |
| **Result summary** |
| **Genetic diagnosis of *BRCA1*-related, reduced penetrance, cancer susceptibility** |

**Result**

This individual is heterozygous for a germline pathogenic, reduced penetrance *BRCA1* missense variant (details below). Heterozygous *BRCA1* pathogenicvariants cause cancer susceptibility, particularly breast and ovarian cancer in females (OMIM: XXX).

**Implications**

Each of their offspring would be at 50% risk of inheriting this variant and genetic predisposition to *BRCA1-*related cancers. Other relatives are also at increased risk.

**Recommended action**

This patient is at increased risk of developing further *BRCA1*-related cancers. This variant is associated with reduced penetrancecompared to typical *BRCA1* pathogenic variants, therefore patients should be managed appropriately, based on their personal and family history1. We recommend referral to Clinical Genetics where predictive and diagnostic testing for this variant in their relatives can be arranged.

Date issued: <AUTHORISEDDATE> Authoriser: Clinical Scientist

1. Moghadasi et al 2017 PMID: 28490613

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**TECHNICAL INFORMATION**

**Variant details**

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| --- | --- | --- | --- | --- |
| Gene | Zygosity | HGVS description | Location: GRCh37 (hg19) | \*Classification |
| *BRCA1* | Heterozygous | NM\_007294.4:c.5096G>A p.(Arg1699Gln) | Chr17(GRCh37):g.41215947C>T | Pathogenic, Reduced Penetrance |

**Test methodology**

1. Genes screened in the panel: *BRCA1; BRCA2;* *PALB2, ATM, CHEK2* (all coding exons & exon-intron boundaries). **For *ATM* & *CHEK2* genes only clearly truncating variants (nonsense, frameshift, ±1/2 splice & CNVs) in these genes, plus the *ATM* c.7271T>G p.(Val2424Gly) pathogenic missense variant, are reported.**
2. Methodology including sensitivity, CNV detection, Bioinformatics pipeline etc e.g. Enrichment method: Agilent SureSelect Custom Design and sequenced on the Illumina platform with a sensitivity of at least 95%.The target regions of selected transcripts is covered to a minimum read depth of 30x.
3. Screening for large deletions and duplications is performed using comparative depth of coverage of NGS data. Deletions/duplications are confirmed by Multiplex Ligation-Dependent Probe Amplification (MRC-Holland).
4. Limits of detection e.g.NGS technical sensitivity may be reduced for genes with pseudogenes or paralogs, and copy-number variation >xx nucleotides.
5. \*Variant classification – see Appendix 1 overleaf
6. Only clinically relevant results are shown; full details of methods and results, including benign/likely benign variants and variants of uncertain clinical significance with limited evidence, are stored on file and are available on request.

**Sample details**

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| Your lab ref: | 122001180 |  |  |
| Sample ID | 1234567 | Sample collected: | 05 Jun 2020 |
| Sample type | DNA from peripheral blood | Sample received | 05 Jun 2020 |

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| --- | --- | --- |
| Dr xxx | **Patient Name:** | **Jane DOE** |
| Consultant | Gender: | Female |
| <<Hospital address>> | Date of Birth: | 14 Jan 1968 |
| NHS No: | 123 456 7890 |
| Hospital No: | NK |
| Your ref: | GC12345 |

**Appendix 1: Variant classification**

**Variant details**

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| --- | --- | --- | --- | --- | --- | --- | --- |
| Gene | Zygosity | | HGVS description | | Location: GRCh37 (hg19) | \*Classification | |
| *BRCA1* | Heterozygous | | NM\_007294.4:c.5096G>A p.(Arg1699Gln) | | Chr17(GRCh37):g.41215947C>T | Pathogenic, Reduced Penetrance | |
| Gene-Disease Association | | | | Hereditary cancer susceptibility OMIM XXX | | | |
| Inheritance | | | | Autosomal Dominant | | | |
| **Evidence for variant classification using ACMG/AMP guidelines\***: | | | | | | | Evidence points^ |
| PS3\_str  PS4\_str$  PP3\_sup  PM3\_mod | | Bouwman functional assay = deleterious x3 assays  Significant enrichment in cases vs controls. Moghadasi et al 2017 - ENIGMA study of 129 p.(Arg1699Gln) families: pathogenic with intermediate risk for BC and OC (RR 2.83 BC & 5.83 OC). Cumulative risk of BC 20% & OC 6%.  REVEL 0.785  Keupp et al 2019 - found in patient with mild FA-like phenotype and early onset BC | | | | | 4  4  1  2 |
| Total: 11 |

^Evidence point ranges: VUS: 0-5 (10-90% posterior probability pathogenicity); Likely pathogenic: 6-9 (90-99% posterior probability); Pathogenic: >10 (>99% posterior probability). Points awarded per evidence weighting: sup (supporting) = 1, mod (moderate) = 2, str (strong) = 4, vstr (very strong) = 8 (Tavtigian et al 2020 PMID: [32720330](https://pubmed.ncbi.nlm.nih.gov/32720330/); Garrett et al 2020 PMID: [33208383](https://pubmed.ncbi.nlm.nih.gov/33208383/); [ACGS 2020 variant guidelines](http://www.acgs.uk.com/quality/best-practice-guidelines))

\*Variant classification according to the American College of Medical Genetics and Genomics (ACMG)1 and Association for Clinical Genomic Science (ACGS) 2020 guidelines2 and Cancer Variant Interpretation Group-UK BRCA1/2 gene-specific and consensus specification for Cancer Susceptibility Genes3 (<https://www.cangene-canvaruk.org/canvig-uk>; [http://www.canvaruk.org](http://www.canvaruk.org/)/)

1Richards *et al.* (2015) Genetics in Medicine 17:405-24. (PMID: [25741868](https://pubmed.ncbi.nlm.nih.gov/25741868/))

2 [www.acgs.uk.com/quality/best-practice-guidelines](file:///C:\Users\dnamd\AppData\Local\Microsoft\Windows\INetCache\Content.Outlook\F1S86UOM\www.acgs.uk.com\quality\best-practice-guidelines)

3 Garrett et al (2020) J Med Genet (PMID: [32170000](https://pubmed.ncbi.nlm.nih.gov/32170000/))

$ Based on OR from ClinGen Hereditary Breast, Ovarian and Pancreatic Cancer Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ATM Version 1.1 Expert Panel Page: <https://www.clinicalgenome.org/affiliation/50039>;<https://clinicalgenome.org/site/assets/files/7451/clingen_hbop_acmg_specifications_atm_v1_1.pdf>