

***Trust Logo***

**<GLH region name>**

**NHS Genomic Laboratory Hub**

|  |  |  |
| --- | --- | --- |
| ***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**

|  |  |  |
| --- | --- | --- |
| 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**

Predictive testing. <<Referral reason>>

|  |
| --- |
| **Result summary** |
| **At elevated risk (reduced penetrance) of *BRCA1*-associated cancers.** |

**Result**

This individual is heterozygous for the germline familial *BRCA1* pathogenic, reduced penetrance missense variant (details below). Heterozygous <*GENE*> pathogenic variants cause cancer susceptibility (OMIM: xxx), particularly breast and ovarian cancer in females. Compared to typical pathogenic *BRCA1* variants, this variant is associated with a reduced risk of breast and ovarian cancer.

**Implications**

Other relatives may have up to a 50% risk of inheriting this variant and genetic predisposition to *BRCA1*-associated cancers.

**Recommended action**

This individual is at increased risk of developing *BRCA1-*associated 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 her relatives can be arranged.

Date issued: <AUTHORISEDDATE> Authoriser: Clinical Scientist

1. Moghadasi et al 2017 PMID: 28490613

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**TECHNICAL INFORMATION**

**Familial variant details**

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

**Test methodology**

1. METHODOLOGY e.g. Genomic DNA Sanger sequencing with direct chromatogram check: >95% sensitivity
2. 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 for pathogenicity and are available on request.
3. 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 consensus specification for Cancer Susceptibility Genes3 ([http://www.canvaruk.org](http://www.canvaruk.org/)/)

1Richards *et al.* (2015) Genetics in Medicine 17:405-24. (PMID 25741868) 2[www.acgs.uk.com/quality/best-practice-guidelines](file://3PA0-DATA-SERVER/DATA/SCH/GEN/DNA/SHARED/DNA/Hereditary%20cancers/Service%20Management/HC%20report%20examples/CanVIG%20report%20templates%202020/www.acgs.uk.com/quality/best-practice-guidelines)

3 Garrett et al (2020) J Med Genet (PMID: 32170000)

**Sample details**

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

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 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>)

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>