

***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**

|  |  |  |
| --- | --- | --- |
| 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

|  |
| --- |
| **Result summary** |
| **Inconclusive result – consider further action** |

**Result**

This individual is heterozygous for a germline *<GENE>* missense/truncating/splice/copy number variant of uncertain significance (details below).

**Implications**

This finding in isolation is insufficient to justify a change in clinical management.

**Recommended action**

To aid variant re-classification, further evidence is required.

We recommend referral to Clinical Genetics for familial segregation analysis/(RNA studies/etc) if appropriate.

Predictive testing is not indicated for relatives.

Further evidence may become available about this variant in the future: if new clinical decisions based on this variant are required for this family, please request the laboratory to review this variant.

Date issued: <AUTHORISEDDATE> Authoriser: Clinical Scientist

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**TECHNICAL INFORMATION**

**Variant details**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Gene | Zygosity | HGVS description | Location: GRCh37 (hg19) | \*Classification |
| *GENE* | Heterozygous  | NM\_xxx:c.xxxT>G | Chr17(GRCh37):g.xxxxxxA>C | Variant of uncertain significance |

**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 region of those 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 | 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 |
| *<GENE>* | Heterozygous  | NM\_xxx:c.xxxT>G p.xxx | Chr17(GRCh37):g.xxxxxxA>C | Variant of uncertain significance |
| Gene-Disease Association | Hereditary cancer susceptibility OMIM xxx |
| Inheritance | Autosomal Dominant  |
| **Evidence for variant classification using ACMG/AMP guidelines\***:  | Evidence points^ |
| PM2\_modPS4\_modPP3\_sup | Not on gnomad [<weblink>](https://gnomad.broadinstitute.org/variant/17-41249298-A-C)XXX et al 2003 (PMID:XXX); XXX et al 2016 (PMID:xxx); LOVD/BRCAshare x3Revel score >0.7 | 2 |
| 2 |
| 1 |
| Total: 5 |

^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/>) and 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>4

1Richards *et al.* (2015) Genetics in Medicine 17:405-24. (PMID 25741868) 2[www.acgs.uk.com/quality/best-practice-guidelines](file:///%5C%5C3PA0-DATA-SERVER%5CDATA%5CSCH%5CGEN%5CDNA%5CSHARED%5CDNA%5CHereditary%20cancers%5CService%20Management%5CHC%20report%20examples%5CCanVIG%20report%20templates%202020%5Cwww.acgs.uk.com%5Cquality%5Cbest-practice-guidelines)

3 Garrett et al (2020) J Med Genet (PMID: 32170000); <https://www.cangene-canvaruk.org/canvig-uk> 4<https://clinicalgenome.org/site/assets/files/7451/clingen_hbop_acmg_specifications_atm_v1_1.pdf>