

***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/splice variant of uncertain significance (details below).

**Implications**

This testing detects >99% of pathogenic variants in these genes. This result does not exclude a diagnosis of autosomal dominant hereditary ovarian cancer. As this individual does not have a detectable pathogenic variant in *BRCA1* or *BRCA2*, PARP inhibitor therapy is not currently indicated by this test in isolation.

**Recommended action**

We recommend testing of the tumour if this individual is still being considered for treatment with PARP inhibitors as ~7% of high grade serous ovarian/fallopian tube/peritoneal cancers have a somatic *BRCA1* or *BRCA2* pathogenic variant (Frugtniet *et al* 2021 PMID: 34657373).

To aid variant re-classification, further evidence is required. We recommend referral to Clinical Genetics for familial segregation analysis/(RNA studies/etc) if appropriate. 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.

Authoriser: Clinical Scientist Date issued: <AUTHORISEDDATE>

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**TECHNICAL INFORMATION**

**Variant details**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Gene | Zygosity | HGVS description | Location: GRCh37 (hg19) | \*Classification |
| *<GENE>* | Heterozygous | NM\_007294.3(BRCA1):c.xxxT>G | Chr17(GRCh37):g.xxxxxxA>C | Variant of uncertain significance |

**Test methodology**

1. Genes screened in the panel: *BRIP1; BRCA1; BRCA2; MLH1; MSH2; MSH6; PALB2; RAD51C; RAD51D* (all coding exons & exon-intron boundaries)
2. 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. \*Variant classification – see Appendix 1 overleaf
5. NGS technical sensitivity may be reduced for genes with pseudogenes or paralogs, and for copy-number variation >20 nucleotides.
6. Only clinically relevant results are shown; full details of methods and results, including benign/likely benign variants and variants of uncertain clinical significance, are stored on file and are available on request.

**Sample details**

|  |  |  |  |
| --- | --- | --- | --- |
| Your lab ref: | 122001180 |  |  |
| Sample ID | 1234567 | Sample collected: | 05 Jun 2020 |
| Sample type | 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**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Gene | Zygosity | | HGVS description | | Location: GRCh37 (hg19) | \*Classification | |
| *<GENE>* | Heterozygous | | NM\_xxx(GENE):c.xxxT>G p.xxx | | ChrXX(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\_mod  PS4\_mod  PP3\_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  Revel 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 gene-specific and consensus specification for Cancer Susceptibility Genes3

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/)) and <https://www.cangene-canvaruk.org/canvig-uk>