

***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* |
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**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: 'test name' (Rxx.x)

**Result summary:** Genetic diagnosis of <GENE>-associated (reduced penetrance) cancer susceptibility. *or*

Consistent with a genetic diagnosis of <GENE>-associated (reduced penetrance) cancer susceptibility.

**Result:** This individual is heterozygous for a germline <likely> pathogenic, reduced penetrance <GENE> <missense/splice> variant (details below). Heterozygous <GENE> pathogenic variants cause cancer susceptibility (OMIM: XXX). Compared to typical pathogenic <GENE> variants, this variant is associated with a reduced risk of <GENE>-associated cancers.

**Implications:** The clinical significance of the variant should be interpreted in the context of the wider family history of cancer. Other relatives may have up to a 50% risk of inheriting this variant and genetic predisposition to <GENE>-associated cancers.

This individual may benefit from PARP inhibitor therapy, if clinically appropriate. [BRCA1/2 PV]

OR

The clinical significance of the variant should be interpreted in the context of the wider family history of cancer. Other relatives may have up to a 50% risk of inheriting this variant and genetic predisposition to <GENE>-associated cancers.

As this individual does not have a detectable pathogenic variant in BRCA1 or BRCA2, this result should be considered along with the relevant tumour testing to determine the degree of benefit with PARP inhibitors if clinically appropriate2. [PV in other genes]

**Recommended action:** This individual is at increased risk of developing further <GENE>-associated cancers. This variant is (<may be>) associated with reduced penetrance, therefore individuals should be managed appropriately, based on their personal and family history. We recommend referral to Clinical Genetics where risk of <GENE>-associated cancers can be discussed and predictive and diagnostic testing for this variant in their relatives can be arranged.

Date issued: <AUTHORISEDDATE> Authoriser: Clinical Scientist

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**TECHNICAL INFORMATION**

**Variant details**

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

1. Genes screened in R430 panel: ATM, BRCA1, BRCA2, CHEK2, MLH1, MSH2, MSH6, PALB2 (all coding exons and exon-intron boundaries). For ATM & CHEK2, 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.The PARP inhibitor olaparib is recommended for use within the Cancer Drugs Fund as an option for maintenance treatment of BRCA mutation-positive metastatic castration-resistant prostate cancer [www.nice.org.uk/guidance/gid-ta887].

3.Enrichment method: Agilent SureSelect Custom Design and sequenced on the Illumina platform with a sensitivity of at least 95% for heterozygous SNVs. Low level/mosaic variants below 10% are not detected. The target region of selected transcripts is covered to a minimum read depth of 30x.

4.Screening for large deletions and duplications is performed using comparative depth of coverage of NGS data. The sensitivity of copy number variant detection may be reduced for exons with a high GC content. Deletions/duplications are confirmed by Multiplex Ligation-Dependent Probe Amplification (MRC-Holland).

5.Variant nomenclature and classification - see Appendix 1 overleaf. Only 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.