Test results

12 Gene Breast Cancer Panel

Patient name	Example	Sample collection date	01/02/2023
Date of birth	03/03/1993	Sample accession date	03/02/2023
Sex at birth	Female	Report date	17/02/2023
Requesting physician	Dr James Mackay	BSPS lab number	23D001
Sample type	Saliva	Everything Genetic barcode	12345678910

Test performed

Everything Genetic 12 Gene Breast Cancer Panel

Reason for testing

Cancer - Personal history (specified below)

Personal history of breast cancer

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Result: POSITIVE

A pathogenic mutation has been identified in:

Gene	Variant	Zygosity	Variant classification
BRCA2	c.755_758del p.(Asp252Valfs*24)	Heterozygous	Pathogenic

About this test

This test evaluates 12 genes for variants (genetic changes) that are associated with Hereditary Breast and Ovarian Cancer (HBOC). Genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk of developing breast or ovarian cancer, support a clinical diagnosis, and assist with the development of personalised treatment and management.

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Clinical interpretation

The BRCA2 variant c.755_758del p.(Asp252Valfs*24) creates a shift in the reading frame starting at codon 252. The new reading frame ends in a stop codon 23 positions downstream. According to HGMD Professional 2019.4, this variant has previously been described as disease causing for breast cancer by Tavtigian et al., 1996 (PMID: 8589730), Schrader et al., 2016 (PMID: 26556299), Park et al., 2017 (PMID: 28111427). ClinVar lists this variant as pathogenic (clinical testing/research, Variation ID: 38103). It is classified as pathogenic (class 1) according to the recommendations of CENTOGENE and ACMG (please see additional information below).

Pathogenic germline variants in the BRCA2 gene are associated with familial breast-ovarian cancer type 2, also known as hereditary breast and ovarian cancer syndrome (HBOC), an autosomal dominant disorder. It is characterised with an increased life-time risk for breast cancer (38%-84%), ovarian cancer (16.5%-27%), prostate cancer (15%), and pancreatic cancer (2%- 7%), and possibly also melanoma.

Breast cancer is one of the most common forms of cancer, accounting for about 25% of all cancers in women. It is 100 times more common in women than in men, although men tend to have poorer outcomes due to delays in diagnosis. About 5 to 10% of all breast cancers are inherited, and most of them are associated with BRCA1 and BRCA2 genes. BRCA1/BRCA2 germline mutations might also have implications in cancer therapy which should be discussed with the oncologist/gynaecologist (OMIM®:612555).

CENTOGENE variant classification (based on AMCG recommendations)

Class 1 – Pathogenic
Class 2 – Likely pathogenic
Class 3 – Variant of unknown significance (VUS)
Class 4 – Likely benign
Class 5 – Benign

Additionally, other types of clinically relevant variants can be identified (e.g., risk factors, modifiers).

Genes analysed

This table represents a complete list of the genes analysed for this individual:

ATM	BRCA1	CDH1	PALB2	RAD51C	STK11
BARD1	BRCA2	CHEK2	PTEN	RAD51D	TP53

Method

Genomic DNA is enzymatically fragmented and regions of interest are enriched using DNA capture probes. The final indexed libraries are sequenced on an Illumina platform. The coding regions of the panel genes, 10 bp of flanking intronic sequences, and known pathogenic/likely pathogenic variants within these genes included in the enrichment design (coding and non-coding), are targeted for analysis. Data analysis, including alignment to the hg19 human reference genome (Genome Reference Consortium GRCh37), variant calling, and annotation is performed using CentoCloud, a Software as a Service platform that is able to collate information from internal and external reference databases to identify, prioritise and classify genetic variants associated with oncological diseases as to their pathogenicity using ACMG guidelines.

Variants of unknown significance (VUS) will be reported unless the described phenotype(s) is already explained by a detected pathogenic or likely pathogenic variant(s) or the detected VUSs are not related to the described phenotype(s).

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The Copy Number Variation (CNV) detection software has a sensitivity of more than 95% for all homozygous/hemizygous deletions, as well as heterozygous deletions/duplications and homozygous/hemizygous duplications spanning at least three consecutive exons.

Limitations

The genetic results are interpreted in the context of the provided clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the provided genetic data or patient information is inaccurate and/or incomplete. If the obtained genetic results are not compatible with the clinical findings, additional testing should be considered.

More complex genetic events such as inversions, translocations, and repeat expansions, are not analysed in this test. In addition, due to technology limitations, certain regions may be poorly covered, or not covered at all. In these regions and others encompassing repetitive, high homology (such as pseudogene homology), and GC-rich sequences, relevant variants can be missed.

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Potential aberrant splicing is assessed with splice prediction tools. Intronic variants that are beyond 10 nucleotides from exon-intron boundaries are not considered for aberrant splicing analysis, with the exception of known pathogenic splicing variants evidenced by external sources.

Disclaimer

Full exon coverage of all genes is not available and therefore some variants may not be detected.

As with all complex technical analyses, there are potential sources of error, including certain genetic variants in primer annealing sites, inhibitory contaminants in the genomic DNA extracted from the patient sample, technical issues, lower than expected coverage of certain amplicons due to the genomic sequence, changes to the classification of variants, changes to the database used for the annotation of variants, and recent clinical research. This assay should not be used for diagnosis in isolation, but rather used in conjunction with a medical diagnosis, family history and treatment plan provided by a qualified clinician. The assay was performed by Berkshire and Surrey Pathology Services (BSPS) and is currently part of an Extension to Scope application to UKAS under ISO15189:2012 standards.

The data analysis is performed and validated by CENTOGENE GmbH; the requested genetic testing itself is based on the highest and most current scientific and analytical standards. However, in very few cases genetic tests may show an incorrect result, e.g., because of the quality of the material provided or where a test fails for unforeseeable or unknown reasons that cannot be influenced by the test provider in advance.

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This report has been reviewed and approved by:

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Date: 17/02/2023

Authorised BSPS signature

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Berkshire and Surrey Pathology Services is accredited by UKAS to BS EN ISO15189:2012.

Signed on behalf of Everything Genetic Ltd

Dr James Mackay, MA, MD, FRCP, FRCPE
Medical Director

Date: 17/02/2023

Authorised signature

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