BRCAgermline

Clinical Testing Cert. No. 822

Genekor Medical S.A. | 52, Spaton Ave., 15344, Gerakas, Athens, Greece ,G.E.MI. nr: 0007856001000
email: info@genekor.com, www.genekor.com | Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

SAMPLE INFORMATION

Name :	XXX	**Date Received :**	XXX
Medical ID :	XXX	**Date of Report :**	XXX
Date of Birth :	XXX	**Req. Physician :**	XXX
Location :	XXX	**Barcode :**	XXX
Material :	XXX	**Sample acceptability :**	XXX

Mutation detection of Single Nucleotide Variation (SNV) and Large Genomic Rearrangements (LGRs) in the *BRCA1* and *BRCA2* genes by Next Generation Sequencing and MLPA

Result

***BRCA1* - The clinically significant variant NM_007294:c.5266dup, p.(Gln1756Profs*74) was identified in the *BRCA1* gene, in heterozygosity.**

This mutation is an insertion of one nucleotide (cytosine), resulting in a frameshift and the creation of a novel translational termination codon after 74 amino acid residues. The protein product thus produced is truncated and non-functional. This mutation has been described in the international bibliography (http://research.nhgri.nih.gov/projects/bic) and has been shown to be a founder mutation in a number of ethnic groups (PMID: 12142080). The mutation database ClinVar contains entries for this variant (Variation ID: 17677). For these reasons, this variant is classified as pathogenic. According to international guidelines it is recommended that relatives of the patient are tested for the above mutation.

***BRCA2* - No known pathogenic mutation or rearrangement identified**

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Interpretation

The *BRCA1* gene involved in the homologous recombination complex (HR) and is associated with autosomal dominant hereditary breast and ovarian cancer (HBOC) syndrome. This result is consistent with a predisposition to, or diagnosis of, *BRCA1*-related conditions. HBOC syndrome is characterized by an increased lifetime risk for breast cancer, contralateral breast cancer, male breast cancer, ovarian cancer, prostate cancer, pancreatic cancer, and other cancers (PMID: 12237281).The lifetime risk for female breast cancer in individuals with a pathogenic *BRCA1* sequence change is 40-87% (PMID: 10498392). The risk for contralateral breast cancer in these individuals is up to 43% within ten years of the initial breast cancer diagnosis (PMID: 15197194). The lifetime risk for male breast cancer in individuals with a pathogenic *BRCA1* sequence change is 1.2% (PMID: 18042939). The lifetime risk for ovarian cancer, fallopian tube, or peritoneal cancer in females is 16-44% (PMID: 23628597). Clinical management guidelines for HBOC syndrome can be found at www.nccn.org.

The *BRCA2* gene involved in the homologous recombination complex (HR) and is associated with autosomal dominant hereditary breast and ovarian cancer (HBOC) syndrome and autosomal recessive Fanconi anemia. The lifetime risk for contralateral breast cancer in individuals with a single pathogenic *BRCA2* variant is 23% within 5 years of the primary breast cancer (PMID: 24764694,14576434,10498392). The lifetime risk for ovarian, fallopian tube, or peritoneal cancer is 16-27% (PMID: 9497246, 9145676). The risk for male breast cancer in individuals with a pathogenic *BRCA2* mutation is 7-8% (PMID: 27144062). There are also increased risks for melanoma, prostate cancer (20%), and pancreatic cancer (2-3%) (PMID: 10433620).
Clinical management guidelines for individuals carrying pathogenic variants in the *BRCA2* gene can be found at www.nccn.org.

Patients with germline mutations in HR genes may benefit from platinum based therapies (PMID: 20406929) and treatment with PARP inhibitors (PMID: 31218365).

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Methodology

Genomic DNA was extracted from the sample under investigation and was analyzed by a solution based capture approach using a custom target enrichment panel containing the *BRCA1* and *BRCA2* genes (KAPA HyperExplore Max 3Mb T1, NimbleGen, Roche). Sequencing was carried out using MGI technology. Reads were aligned to the reference sequence (GRCh37), and sequence changes were identified and interpreted in the context of a single clinically relevant transcript. All clinically significant observations were confirmed by Sanger Sequencing. Unless otherwise indicated, all targeted regions were sequenced with ≥20x depth. This assay targets all coding regions of the indicated transcript and 20 base pairs of flanking intronic sequence.

The presence of large genomic rearrangements (LGRs), is investigated using the commercial computational algorithm SeqPilot Version 4.4 Build 505 (JSI Medical System) and the computational algorithm panelcn.MOPS (PMID: 28449315). The presence of LGRs is verified by use the MLPA* method (Multiplex Ligation- dependent Probe Amplification, *BRCA1*: P002, *BRCA2*: P045, MRC Holland; PMID:12060695)

*Note:

Mutations resulting in incorrect maturation of messenger RNA are not detectable with used methodology. Also mutations in other genes like *PALB2, BARD1, CDH1* etc are not excluded.

The method used cannot detect low-level mosaicism (with coverage <25%). The method used achieves 99% sensitivity and specificity for single nucleotide variants and insertions and deletions <15bp. Sensitivity to detect genomic rearrangements larger than 15bp but smaller than a full exon may be reduced. Balanced genomic rearrangements cannot be detected.

Every molecular test has an internal 0.5-1% chance of failure. This is due to rare molecular events and factors related to the preparation and analysis of the samples.

GeneKor MSA is accredited by **ISO15189:2012 (Cert.no 822)** to carry out analysis of the ***BRCA1*** and ***BRCA2*** genes by **MLPA**

Genekor 's clinical laboratories are accredited by **ISO15189:2012 (Cert.no 822)** and certified by **CAP (College of American Pathologists)** and **EMQN (European Molecular Genetics Quality Network)** for the analysis of ***BRCA1*** and ***BRCA2*** by both Sanger sequencing and Next Generation Sequencing by Devyser or Nimblegen, Roche.

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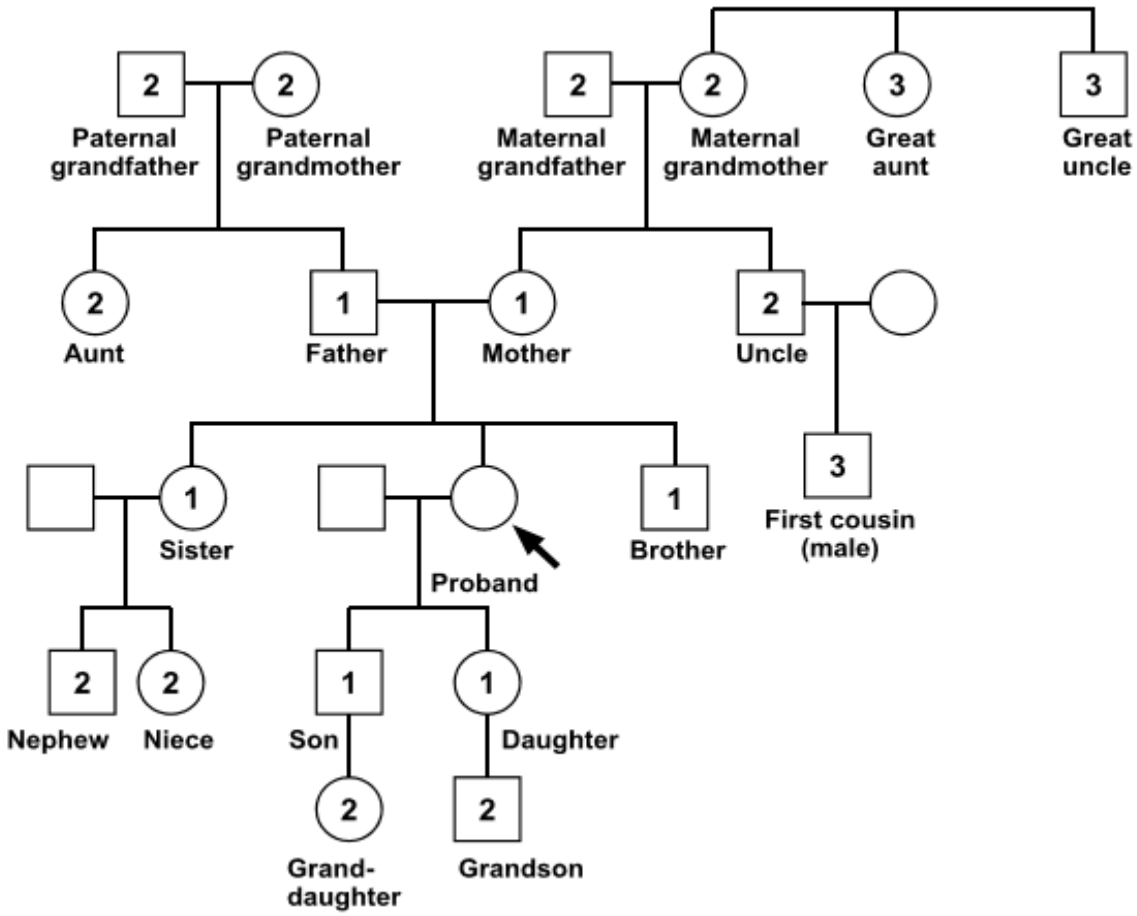
Family tree



Note: **The information shown on the family tree has been provided by the patient and not by medical records.**

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Scientific Director: George Nasioulas PhD

Name: **TUNCAY YAHYA ADIL** Barcode: **22013332TR** Location: -

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