SAPIENS SG GENETIC DISEASES DIAGNOSTIC CENTER
MEDICAL ANALYSIS REPORT
LABORATORY LICENSE NO: GHDM-SM/34.39/01

Patient Name	:	**Sampling Location**	:
Gender	:	**Test Request Date**	:
Date Of Birth	:	**Sample Collection Date**	:
ID Number	:	**Sample Acceptance Date**	:
Protocol Number	:	**Report Approval Date**	:
Sample Number	:	**Report Release Date/Report Number**	:
Sample Type	:		

Refering Center / Physician :

Reason For Referral :

Test Name: Hereditary Breast Ovary Panel (BRCA 1-2)

Method: Next Generation Sequencing Analysis (NGS)

Used Platform: Illumina Miseq

Used Kits: BRCA MASTR Dx Kit, Multiplicom

Bioinformatics Analysis: Sophia DDM®

ANALYSIS RESULTS:

SNV / INDEL Analysis:
POSITIVE, **Heterozygous for *BRCA1* (NM_007294.4) c.5137del (p.Val1713*) pathogenic variant was detected.** No pathogenic variants detected in the *BRCA2* gene.

INTERPRETATION:

Heterozygous pathogenic c.5137del (p.Val1713*) variant was detected in *BRCA1* gene.

The c.5137del (p.Val1713*) variant is a deletion that causes a stop codon at position 1713 in the protein. Loss-of-function variants in *BRCA1* are known to be pathogenic (PMID: 20104584). ClinVar database classifies this variant as 'Pathogenic' related to Breast-ovarian cancer, familial, susceptibility to, 1 syndrome (ClinVar ID: 55411). dbSNP database classifies this variant as 'Pathogenic' (dbSNP: rs80357997). This variant is present with low frequency in population databases (gnomAD: 0.00000398). According to ACMG criterias[1], this variant is classified as **'pathogenic'**.

The patient has an elevated/high lifetime risk of developing further *BRCA1*-related cancers.

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The *BRCA1* gene encodes a protein that plays an important role in DNA repair, control of cell cycle checkpoints, and maintenance of genomic stability. This protein is a tumor suppressor protein that plays a role in forming the BRCA1-related genome surveillance complex (BASC), together with other tumor suppressors, DNA damage sensor and signal transmitters. The germline pathogenic variants in the *BRCA1* gene cause more than 60% risk for breast cancer, 7–26% risk for prostate cancer and 39-58% risk for ovarian cancer[2].

Variant Table:

Gene (Reference Sequence)	**Variant**	**Classification¶**	**Status**
BRCA1 (NM_007294.4)	c.5137del (p.Val1713*)	Class 5 (Pathogenic)	Heterozygous

¶ Variant class is determined based on American College of Medical Genetics and Genomics (ACMG) criterias.

RECOMMENDATIONS:

1. Since the *BRCA1* pathogenic variant has been detected in a heterozygous form,
    a. *BRCA1* gene is included in the NCCN guideline[2] in terms of breast, ovary, pancreas, skin and prostate cancer risk. **The patient is a candidate for risk reduction approach.**
    b. It is recommended that age-appropriate follow-up-check-up criteria should be planned with a multidisciplinary approach, considering the *BRCA1* variant carriage.
    c. It is an autosomal recessive Fanconi anemia, complementation group S gene. Genetic counseling is recommended in terms of recessive disease carrier.
2. Copy number variations (CNVs) in the tested genes are not screened with this method. CNV screening using a method such as MLPA is recommended.
3. It is recommended that the findings be evaluated together with the patient's clinical and other laboratory data.
4. Genetic councelling is recommended.

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5. Molecular testing of other relevant family members is possible following appropriate genetic councelling.
6. NCCN treatment guidelines for BRCA-related cancers (Breast, Ovarian, Pancreatic Adenocarcinoma, Prostate) now recommend treatment with PARP (poly ADP-ribose polymerase) inhibitors for patients with germline or somatic BRCA1/2 Pathogenic/Likely Pathogenic variants, as PARP inhibitors have been demonstrated to be active in these patients. These agents include olaparib and rucaparib for metastatic castration-resistant prostate cancer that has progressed following previous treatment (NCCN Guidelines®)[2].

QUALITY CONTROL RESULTS

Target region's average coverage:	700x	**Target region's minimal 25X coverage:**	%100
Target region's minimal 50X coverage:	%100	**Target region's minimal 100X coverage:**	%100

TECHNICAL SPECIFICATIONS and LIMITATIONS:

BRCA MASTR Dx Kit, Multiplicom, is Next Generation Sequencing (NGS) panel designed to detect SNV/Indel variants in breast and ovarian cancer associated *BRCA1* and *BRCA2* genes. This method is based on the stages of PCR (Polymerase Chain Reaction) amplification of disease related gene region(s) and sequencing with NGS. Sequencing reactions are performed using kits compatible with Illumina NextSeq® or Myseq systems. Raw data is analyzed with Sophia DDM® platform. For alignment and variant calling was performed using reference genome GRCH37/Hg19. For variant classification HGMD Public and ClinVar databases and databases created by Maxwell et al. were used. For variants not found in other databases, criteria created by Maxwell et. al were used. These criteria were based on ACMG's (American College of Medical Genetics and Genomics) variant classification guideline.

All coding exons and exon-intron boundaries of the gene(s) considered in the test are included in the kit up to 20 bases unless otherwise stated. Other intronic regions are not covered by the test. Limitations of next generation

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sequencing technique like error reads in single nucleotide repeat regions are valid to current method as well. Copy number variations were not tested in this method; *BRCA1* and *BRCA2* genes, in which intragenic deletions and duplications are particularly important, should be tested separately with a different method such as MLPA. Pseudogene regions, homopolymer regions that resemble or overlap the gene were excluded from the analysis. 5' and 3' UTR, downstream and upstream regions were excluded from analysis because there is not enough evidence on their relevance in the literature. In peripheral blood samples the variants with low variant fraction (VF) of 20% or less, low sensitivity and specificity, classified as benign/likely benign and common in healthy populations may not have been reported. and deep intronic variants are not considered unless listed in mentioned databases as disease causing variants. The negative result given in the report does not exclude the presence of the mentioned disease. There may be another gene that causes the same disease outside of the test panel, or there may be a gene or gene region that has not yet been associated with the disease.

Confirmation of the findings with a different method is recommended in the clinical decision-making process. The entire variant list can be shared, if requested by the clinician. This test was performed from the above-mentioned material type. This sample was sent to our center with the record of the patient mentioned above.

It is recommended to consider the influencing factors involved in preanalytical errors before the material arrives to our institution. The responsibility of this process does not belong to our institution. External laboratory services can be used to finalize the test in accordance with the Regulation on Genetic Diseases Evaluation Centers and ISO 15189 Medical Laboratory Accreditation (Düzen Laboratories Group, Istanbul), and wet laboratory-device usage stages can be performed at different locations. There is the possibility of false positive-negative results within the technical characteristics - limitations of the method used. As with all laboratory tests, clinical findings should be prioritized; If necessary, additional tests / retests should be requested in case of clinical suspicion. It should not be used for decision making alone. Genetic counseling should be recommended before and after the test in all genetic screenings.

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REFERENCES:

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