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: Homologous Recombination Solution by SOPHiA GENETICS

Bioinformatics Analysis: Sophia DDM®

ANALYSIS RESULTS:

SNV / INDEL Analysis:
POSITIVE, **The Tier IA c.5485dup (p.Glu1829Glyfs*51) variant was detected in *BRCA1* gene.** No pathogenic variants detected in the *BRCA2* gene.

INTERPRETATION:

Tier IA	Tier IB	Tier IIC	Tier IID
***BRCA1* (NM_007294.4): c.5485dup (p.Glu1829Glyfs*51)**	**No variant was detected**	**No variant was detected**	**No variant was detected**

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In the study performed on the DNA material obtained from the patient's formalin fixed paraffin embedded sections, **Tier IA c.5485dup (p.Glu1829Glyfs*51)** pathogenic mutation of ***BRCA1*** **(NM_007294.4)** was detected with 49.8% variant fraction.

BRCA-related cancers (Breast, Ovarian, Pancreatic Adenocarcinoma, Prostate; etc.) 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 **niraparib, olaparib, and rucaparib** for chemotherapy-refractory ovarian cancer (NCCN Guidelines ®)[2].

RECOMMENDATIONS:

1. It is recommended that the findings be evaluated together with the patient's clinical and other laboratory data.
2. Genetic councelling is recommended.

TECHNICAL SPECIFICATIONS AND LIMITATIONS:

The technical study was carried out on the Illumina Nextseq with Next Generation Sequencing (NGS) method using SOPHiA GENETICS: Homologous Recombination Solution Kit. For bioinformatic analysis, Sophia DDM®, Switzerland and Human reference genomes of *BRCA1* (NM_007294.4) and *BRCA2* (NM_000059.4) were used. For alignment and variant calling was performed using reference genome GRCH37/Hg19. In the filtering and evaluation of variants, HGMD Public, ClinVar, OMIM®, dbSNP (v151), gnomAD (v2.1.1) databases, in-silico prediction programs such as MutationTaster, SIFT, PolyPhen-2 and REVEL were used. Variants with minor allele frequency below 1% in the population databases such as GnomAD, 1000 Genome, ESP5400 were evaluated. The reported variant is classified according to the

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"[1]ACMG Variant Classification Guideline" and was entitled according to the "[3]HGVS (Human Genome Variation Association) nomenclature". All coding exons and exon-intron boundaries of the gene/s are included in the kit. Pseudogen regions, homopolymer regions that resemble or overlap the gene were excluded from the analysis. A negative result given in the report does not exclude the presence of the aforementioned disease. There may be another gene, out of the test panel that causes the same disease, or there may be a gene or gene region that has not yet been associated with the disease. Confirmation of the findings by a different method during clinical decision-making process is recommended. The entire variant list can be shared, if requested by the clinician.

This test can detect point mutations and small deletions/duplications in coding exons and +/-20 base pair exon-intron boundaries with high sensitivity and specificity. Sensitivity and specificity may vary depending on targeted region's characteristics (e.g., GC rich regions, repeat sequences, homopolymer regions). Synonymous, UTR and deep intronic variants are not considered unless listed in mentioned databases as disease causing variants. Numerical and structural chromosome anomalies, large deletions/duplications, repeat sequence expansions and mitochondrial genome variants cannot be detected by this method. Limitations of next generation sequencing technique like error reads in single nucleotide repeat regions are valid to current method as well. Monoallelic VUS variants detected in this analysis which are related to biallelically (recessive) inherited diseases may not be included in the report. The variants with low variant fraction (VF) of 5% or less, low sensitivity and specificity, classified as benign/likely benign and common in healthy populations may not have been reported.

There is the possibility of false positive-negative results within the technical characteristics - limitations of the method used. 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 that may be involved in pre-analytical errors before the material arrive to our institution. The responsibility of this process does not belong to our institution. The test does not include sample verification. As with all laboratory tests, clinical findings should be prioritized; If

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necessary, additional tests / retests should be requested in case of clinical suspicion. As with all laboratory tests, it should not be used alone as a clinical decision maker. No comment can be made on the adequacy of the analysis, in patients for whom sufficient clinical data is not shared, and additional interpretation/recommendations cannot be made. Genetic counseling should be recommended before and after the test in all genetic screening.

REFERENCES:

1. Richards, Sue, et al. "Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology." Genetics in medicine 17.5 (2015): 405.
2. Li, Marilyn M., et al. "Standards and guidelines for the interpretation and reporting of sequence variants in cancer: a joint consensus recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists." The Journal of molecular diagnostics 19.1 (2017): 4-23.
3. NCCN Guidelines Ovarian Cancer Continue Including Fallopian Tube Cancer and Primary Peritoneal Cancer Version 2.2023 — June 2, 2023
4. NCCN Guidelines Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Version 2.2024 — September 27, 2023

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Reason For Referral :

Dr. Ceyhan Sayar, MD
Medical Geneticist

Assoc. Prof. Dr. Kanay YARARBAŞ, MD
Medical Geneticist

Verification Link:

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