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 Cancer Panel- 59 Genes
Method: Next generation sequencing analysis
Panel Genes: *APC, ATM, AXIN2, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, DDB2, EPCAM, ERCC2, ERCC3, ERCC4, ERCC5, FANCA, FANCC, FH, FLCN, GALNT12, HDAC2, HOXB13, MEN1, MET, MITF, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NF2, NTHL1, PALB2, PMS2, POLD1, POLE, POLH, PTCH1, PTEN, RAD51C, RAD51D, RB1, RET, SMAD4, STK11, TP53, TSC1, TSC2, VHL, WT1, XPA, XPC*
Platform: Illumina Nextseq
Kit: SOPHiA GENETICS: The Custom Hereditary Cancer Solution (CHCS).
Bioinformatics analyses: Sophia DDM®

ANALYSIS RESULTS

SNV/INDEL ANALYSIS	***BRCA1-2* CNV ANALYSIS**
NEGATİVE, **No pathogenic/likely pathogenic[1] variants were detected.** ***[1]Variant classification is determined according to ACMG criteria.***	**NEGATİVE,** **No deletion or duplication was detected.**

INTERPRETATION:

As a result of the analyses, no clinically relevant pathogenic/likely pathogenic variants related to the described phenotype of the patient was identified within the detection capacity of the method used.

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RECOMENDATIONS:

-It is recommended that the obtained findings should be evaluated together with the patient's clinical and other laboratory data, and it should not be used for stand-alone decision making. Take into account sections of Technical Specifications and Limitations. It is recommended that the test management be planned with a multidisciplinary approach.

-Genetic counselling is recommended.

NGS QUALITY CONTROL RESULTS:

Target region's average coverage:	**862x**	**Target region's minimal 25X coverage:**	**%99.99**
Target region's minimal 50X coverage:	**%99.90**	**Target region's minimal 100X coverage:**	**%99.88**

TECHNICAL SPECIFICATIONS and LIMITATIONS:

SOPHiA GENETICS The Custom Hereditary Cancer Solution (CHCS) Kit, is Next Generation Sequencing (NGS) panel designed to detect SNV/Indel variants in 59 genes associated with breast, ovarian, gastric, pancreatic, prostate cancers and melanoma, Lynch, Bloom, Von-Hippel, intestinal polyposis syndromes and Xeroderma Pigmentosum. 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® system. Raw data is analyzed with Sophia DDM® platform. 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, 1000Genome, ESP5400 were evaluated. Detected variants were classified according to the ACMG Variant Classification Guideline (Richards et al., 2015).

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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, 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. Pseudogene regions, homopolymer regions that resemble or overlap the gene were excluded from the analysis. Monoallelic VUS variants detected in this analysis which are related to biallelically (recessive) inherited diseases may not be included in the report. The copy number variants (CNV) for the analysed *BRCA1-2* genes that are performed within the scope of this analysis are based on a software calculation using NGS data. CNV analysis is qualified as a screening test. It has a high sensitivity and a high negative prediction value, so it is not recommended to be confirmed with another method if it is not considered clinically necessary. Although its specificity is also relatively high, it is recommended to be confirmed in case of a positive result. 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. 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. There is the possibility of false positive-negative results within the technical characteristics - limitations of the method used. The test does not include sample verification. As with all laboratory tests, clinical findings should be prioritized; If necessary, additional tests / retests should be requested in case of clinical suspicion. As with all laboratory tests, it should not be used for decision making alone. No comment can be made on the analysis's adequacy, 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. 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

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Accreditation (Düzen Laboratories Group, Istanbul), and wet laboratory-device usage stages can be performed at different locations.

REFERENCES:

- 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.

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