MAYO CLINIC

1-800-533-1710

Hereditary Common Cancer Panel

COMCP

PATIENT NAME				ORDER NUMBER
TESTRNV, IMPLEMENTATION				**L002000263**
PATIENT ID X100366922	DATE OF BIRTH 02/19/1968	AGE 53 Y	SEX Female	REQUESTED BY CLIENT TESTING
COLLECTED 9/2/2021, 7:30 AM	RECEIVED 9/3/2021, 1:57 PM	REPORTED 9/9/2021, 6:15 PM		
The collected, received, and reported dates and times on the report are in the time zone of the performing location.				CLIENT ORDER NUMBER X100366922
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TEST DESCRIPTION

Evaluation of 36 genes associated with hereditary cancer syndromes

SPECIMEN

WB Whole Blood

RESULT SUMMARY

Variants Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
BRCA1 NM_007294.4	p.E23Vfs*17 p.Glu23Valfs*17 c.68_69del Chr17(GRCh37):g.41276045	heterozygous	PATHOGENIC
AXIN2 NM_004655.4	p.R779W p.Arg779Trp c.2335A>T Chr17(GRCh37):g.63530100	heterozygous	VARIANT OF UNCERTAIN SIGNIFICANCE

The following heterozygous PATHOGENIC variant was detected:
BRCA1 (NM_007294.4), p.E23Vfs*17 (p.Glu23Valfs*17), c.68_69del, Chr17(GRCh37):g.41276045

The following heterozygous VARIANT OF UNCERTAIN SIGNIFICANCE was detected:
AXIN2 (NM_004655.4), p.R779W (p.Arg779Trp), c.2335A>T, Chr17(GRCh37):g.63530100

No additional reportable variants were detected within all other tested genes. See the Genes Analyzed section for a complete list of genes evaluated by this assay.

INTERPRETATION

BRCA1 c.68_69del (p.E23Vfs*17), PATHOGENIC
The heterozygous c.68_69del (p.E23Vfs*17) frameshift variant in the BRCA1 gene (MIM:113705) is an established pathogenic variant. Variants in the BRCA1 gene have been associated with autosomal dominant hereditary breast and ovarian cancer (HBOC) syndrome and autosomal recessive Fanconi anemia (1). This result is supportive of a diagnosis

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of hereditary breast and ovarian cancer (HBOC) syndrome for this individual. This result is also supportive of carrier status for Fanconi anemia. Clinical correlation is recommended. Individuals with certain cancers and pathogenic or likely pathogenic variants in genes involved in the homologous recombination repair pathway may show sensitivity to poly(ADP-ribose) polymerase inhibitors (PARPi) and may be eligible for targeted treatments (2).

AXIN2 c.2335A>T (p.R779W), VARIANT OF UNCERTAIN SIGNIFICANCE
The heterozygous c.2335A>T (p.R779W) missense variant in the AXIN2 gene (MIM:604025) is classified as a variant of uncertain significance. Variants in the AXIN2 gene have been associated with autosomal dominant oligodontia-colorectal cancer syndrome. To our knowledge, this variant has not been reported in affected individuals.This variant is absent from large control databases (3)(4). The prediction from multiple in silico tools is inconclusive as to whether this amino acid change impacts protein function. In-silico analyses predict that this variant is unlikely to impact RNA splicing. Taken together, the evidence is not sufficient to determine whether this variant is benign or pathogenic. Therefore, this variant is classified as a variant of uncertain significance.

This result should be interpreted in the context of clinical findings, family history, and other laboratory testing.

Consultation with a genetics professional is recommended for interpretation of this result and to determine whether reproductive risk assessment and familial testing may be of benefit to this family. Genetic testing for family members is available by ordering FMTT / Familial Mutation, Targeted Testing for the specific variant(s) detected. Please contact the laboratory at 1-800-533-1710 or the online test catalog at www.mayocliniclabs.com for information about FMTT.

REFERENCES:
1) GeneReviews: BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer (https://www.ncbi.nlm.nih.gov/books/NBK1247/) (PMID: 20301425)
2) Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol. 2015;33(3):244-250. doi:10.1200/JCO.2014.56.2728 (PMID 25366685)
3) dbSNP: www.ncbi.nlm.nih.gov/snp; Sherry ST, Ward M and Sirotkin K. dbSNP-Database for Single Nucleotide Polymorphisms and Other Classes of Minor Genetic Variation. Genome Res. 1999;9:677-679 (PMID 10447503)
4) gnomAD Browser: gnomad.broadinstitute.org/; Karczewski K, Francioli LC, MacArthur DG, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature. 2020; 581(7809):434-443 (PMID 32461654)

METHOD

Next generation sequencing (NGS) and/or Sanger sequencing is performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known pathogenic variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for indels less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS, multiplex ligation-dependent probe amplification (MLPA), and/or a polymerase chain reaction (PCR)-based quantitative method is performed to test for the presence of deletions and duplications in the genes analyzed. PCR and gel electrophoresis is performed to test for the presence of the 10 Mb inversion of coding exons 1-7 of the MSH2 gene. See the Genes Analyzed field for a list of genes tested.

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There may be regions of genes that cannot be effectively evaluated for sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of select reportable variants was performed by alternate methodologies based on internal laboratory criteria. See www.mayocliniclabs.com COMCP for details regarding genes with regions not routinely covered.

GENES ANALYZED

APC (including promoters 1A & 1B), ATM, AXIN2, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, DICER1, EPCAM (copy number variants only), GREM1 (upstream enhancer region duplication only), HOXB13, MEN1, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NTHL1, PALB2, PMS2, POLD1, POLE, PTEN (including promoter), RAD51C, RAD51D, RET, SMAD4, STK11, and TP53

DISCLAIMER

Clinical Correlations
If testing was performed because of a clinically significant family history it is often useful to first test an affected family member. Detection of a reportable variant(s) in an affected family member would allow for more informative testing of at risk individuals.

To discuss the availability of further testing options or for assistance in the interpretation of these results, Mayo Clinic Laboratory genetic counselors can be contacted at 1-800-533-1710.

Technical Limitations
Next generation sequencing may not detect all types of genomic variants. In rare cases, false negative or false positive results may occur. The depth of coverage may be variable for some target regions, but assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated for sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of select reportable variants was performed by alternate methodologies based on internal laboratory criteria.

Additionally, low level mosaic variants may not be detected.

This test is not designed to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. Please refer to the Targeted Genes and Methodology Details for the Hereditary Common Cancer Panel in the Special Instructions section of the Test Catalog for the most up to date list of genes included in this test.

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Reclassification of Variants Policy
See www.mayocliniclabs.com COMCP for information regarding the laboratory's policy for reclassification of variants.

Variant Evaluation
Variant curation is performed using published ACMG-AMP recommendations as a guideline. Other gene-specific guidelines may also be considered. Variants classified as benign or likely benign are not reported.

Results from in silico evaluation tools may change over time and should be interpreted with caution and professional clinical judgment.

TEST CLASSIFICATION
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

RELEASED BY

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