Germline Cancer Predisposition Panel

Test Description

The MolQ *BRCA* Germline mutation test helps assess your risk of developing cancer by detecting a potentially harmful change (mutation) in *BRCA1* and *BRCA2* genes.

Patient Demographic

Name: Ms. Kawaljeet Kaur
Sex: Female
Date of Birth/Age: 49 years
Disease: Breast Carcinoma

Clinician

Clinician Name: Dr Amish Vora
Medical Facility: HOPE Clinic
Pathologist: Not Provided

Specimen

Booking ID: 011907180174
Site: NA
Sample Type: Blood
Date of Collection: 18-07-2019
Date of Booking: 18-07-2019

CLINICAL SYNOPSIS

Kawaljeet kaur is a known case of breast cancer and has been evaluated for pathogenic variations in the *BRCA1* and *BRCA2* genes.

RESULTS

No pathogenic or likely pathogenic variant causative of the reported phenotype are detected

ADDITIONAL FINDINGS: VARIANT(S) OF UNCERTAIN SIGNIFICANCE (VUS) DETECTED

No variations were detected in the *BRCA1* and *BRCA2* genes. The *BRCA1* and *BRCA2* genes are 100% covered in this assay.

No other variant that warrants to be reported was detected. Variations with high minor allele frequencies which are likely to be benign will be given upon request.

ADDITIONAL INFORMATION

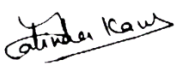
1. *BRCA1* (OMIM #113705) and *BRCA2* (OMIM #600185) genes plays critical roles in DNA repair, cell cycle checkpoint control, and maintenance of genomic stability and functions as a tumor suppressor gene. Susceptibility to hereditary breast-ovarian cancer-type1 and type2 (HBOC) is caused by heterozygous germline mutations in the *BRCA1* and *BRCA2* genes[1].
2. Approximately, 5 -10% of breast and ovarian cancer cases are hereditary, and 85% cases are sporadic[2].
3. In addition to high risk *BRCA1* and *BRCA2* gene variations, there are number of other HBOC predisposing genes such as *ATM, BARD1, BRIP1, CDH1, CHEK2, MSH2, MLH1, MSH6, PMS2, EPCAM, NBN, NF1, MRE11A, PALB2, PTEN, RAD51C, RAD51D, STK11, TP53*, which are recommended to be tested according to NCCN guidelines[2,3].
4. Women with germline heterozygous pathogenic variation in any of homologous recombination repair (HRR) pathway genes that are involved in double strand break (DSB) repair pathway such as *TP53, CHEK2, RAD50, ATM, MRE11A, NBN, NBS1, BARD1, BRIP1, PALB2, RAD51C and RAD51D*, are at an increased lifetime risk for developing breast cancer and ovarian cancer as compared to general population risk which is 12% for breast cancer and 1.3% for ovarian cancer[2].
5. Based on the recent clinical trials (Study-19 and SOLO-2), PARP-inhibitor (Olaparib) has been approved by FDA for the treatment of patients with deleterious or suspected deleterious germline *BRCA1*/2-mutated or homologous recombination repair (HRR) pathway deficient, high grade serous epithelial ovarian cancer who have been treated with three or more prior lines of chemotherapy[4,5].
6. Similarly, another clinical trial (OlympiAD), showed Olaparib treatment to improve progression free survival (PFS) and overall survival (OS) in patients with loss-of-function germline *BRCA1/2*-mutated or homologous recombination repair (HRR) pathway deficient, HER2-negative metastatic breast cancer who have been treated with chemotherapy either in the neoadjuvant, adjuvant, or metastatic setting and has been approved by FDA[6].

RECOMMENDATIONS

- The sensitivity of NGS based assays to detect large heterozygous deletions/duplications, complex rearrangements (>10 bp) and copy number variations (CNVs) is low (70-75%) as it uses short-read sequencing data. Therefore, an alternate method such as Multiplex Ligation-dependent Probe Amplification (MLPA) is recommended to detect such structural variants in *BRCA1* and *BRCA2* genes. Kindly consult with your clinician and contact MolQ Laboratory for this test.
- Genetic counselling is recommended to discuss the implications of the test results.

REFERENCES

1. Online Mendelian Inheritance in Man (OMIM). An Online Catalog of Human Genes and Genetic Disorders., Updated November 21, 2018.
2. Petrucelli N., Daly M. B., Pal T., *BRCA1*- and *BRCA2*-Associated Hereditary Breast and Ovarian Cancer. 1998 Sep 4 [Updated 2016 Dec 15]. In: Adam M. P., *et al.*, editors. Gene Reviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018.
3. National Comprehensive Cancer Network. Genetic/Familial High Risk Assessment: Breast and Ovarian (Version 2.2019).
4. FDA approves Olaparib tablets for maintenance treatment in ovarian cancer. 2017.
5. Moore K., *et al.*, Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2018 Dec 27;379(26):2495-2505.
6. FDA approves Olaparib for germline BRCA-mutated metastatic breast cancer. 2018.



Jatinder Kaur, PhD
Head, Molecular Biology & Genomics

Dr. Gulshan Yadav, MD
Head, Pathology

APPENDIX 1: TEST METHODOLOGY

Method

The *BRCA1*, *BRCA2* gene(s) was/were analyzed by an amplicon-based next-generation sequencing approach. The amplicons cover the entire coding region and the highly conserved exon-intron splice junctions. We have a minimum coverage of >20x for every amplicon. Missing regions or regions of poor quality are completed with classical Sanger sequencing to achieve 100% coverage. Variants of relevance identified by NGS are continuously and individually in-house validated for quality aspects; those variants which meet our internal QC criteria (based on extensive validation processes) are not validated by Sanger.

Genetic test results are reported based on the variant classification recommendations of American College of Medical Genetics[1], as described in the table below:

Variant	A change in a gene. This could be disease causing (pathogenic) or not disease causing (benign).
Pathogenic	A disease causing variation in a gene which can explain the patient's symptoms has been detected. This usually means that a suspected disorder for which testing had been requested has been confirmed.
Likely Pathogenic	A variant which is very likely to contribute to the development of disease however, the scientific evidence is currently insufficient to prove this conclusively. Additional evidence is expected to confirm this assertion of pathogenicity.
Variant of Uncertain Significance	A variant has been detected, but it is difficult to classify it as either pathogenic (disease causing) or benign (non-disease causing) based on current available scientific evidence. Further testing of the patient or family members as recommended by your clinician may be needed. It is probable that their significance can be assessed only with time, subject to availability of scientific evidence.

#The transcript used for clinical reporting generally represents the canonical transcript (according to Ensembl release 87 gene model), which is usually the longest coding transcript with strong/multiple supporting evidence. However, clinically relevant variants annotated in alternate complete coding transcripts could also be reported.
Variants annotated on incomplete and nonsense mediated decay transcripts will not be reported.
#The *in-silico* predictions are based on Variant Effect Predictor, Ensembl release 91 (SIFT version - 5.2.2; PolyPhen - 2.2.2); LRT version - November, 2009 release from dbNSFPv3.1 and Mutation Taster2 based on build NCBI 37 / Ensembl 69.

For any further technical queries please contact contact@molq.in.

DISCLAIMER

- The variants in this report are interpreted based on information available in scientific literature at the time of reporting, therefore, an impact and classification of gene variation might change over time with respect to clinical indication. MolQ Laboratory cannot be held responsible for this, the clinician can request reanalysis of data on an annual basis at an additional cost.
- Variants in untranslated region, promoters and deep intronic regions are not analyzed in this test.
- Incidental or secondary findings (if any) that meet the ACMG guidelines[2] can also be given upon request.
- Test results are interpreted in the context of clinical findings, family history and other laboratory data. In the absence of detailed accurate clinical or family history of the patient, MolQ Laboratory cannot guarantee the accuracy of the interpretation of results.
- The results may be inaccurate in rare circumstances if the individual tested has undergone bone marrow transplantation or blood transfusion.
- MolQ Laboratory is not liable to provide diagnosis, opinion or recommendation related to disease, in any manner. MolQ Laboratory hereby recommends the Patient and/or the guardians of the Patient to contact clinician for further interpretation of the test results.
- This is a laboratory developed test and the development and the performance characteristics of this test was determined by the reference laboratory.

REFERENCES

1. Richards S., *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, 2015 May;17(5):405-24.
2. Green R. C., *et al*., American College of Medical Genetics and Genomics. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing.