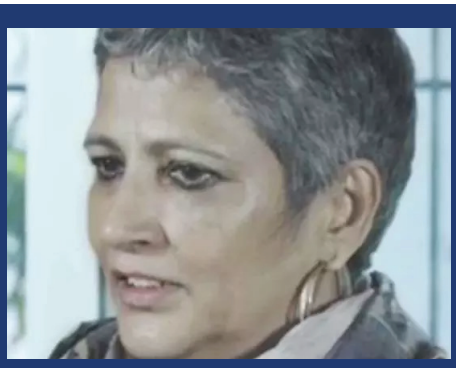
CASE STUDY

Reclassification of a VUS mutation: New Therapeutic Options Revealed



Gender: Female

Age: 52 years

Location: Delhi, NCR Region

Diagnosis: Ovarian Cancer

Strand Test: Germline

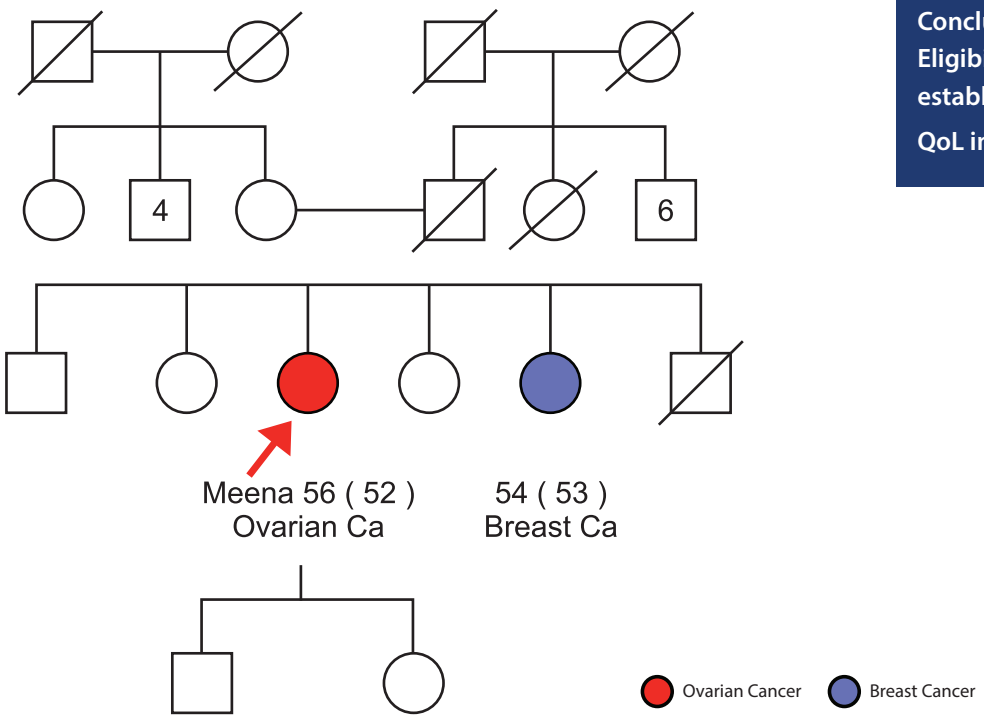
Conclusion:
Eligibility for PARP inhibitor therapy established,
QoL improved for patient

Patient Profile

Meena*, a 56-year-old woman was diagnosed with ovarian cancer at 52 years of age.

She was prescribed platinum-based chemotherapy. Meena's younger sister had been diagnosed with breast cancer at the age of 53 years. Meena was prescribed the Strand Germline Cancer Test to understand her genetic profile and therefore the need to test any family members.

Family Tree- Pre-test Genetic Counselling



Genetic Analysis

The Strand Germline Cancer Test revealed that Meena had a *BRCA2* mutation.

*Name and other details shared post patient and doctor consent

RESULT VUS

A heterozygous 'variant of unknown significance' (VUS) was detected in exon 17 of the *BRCA2* gene.

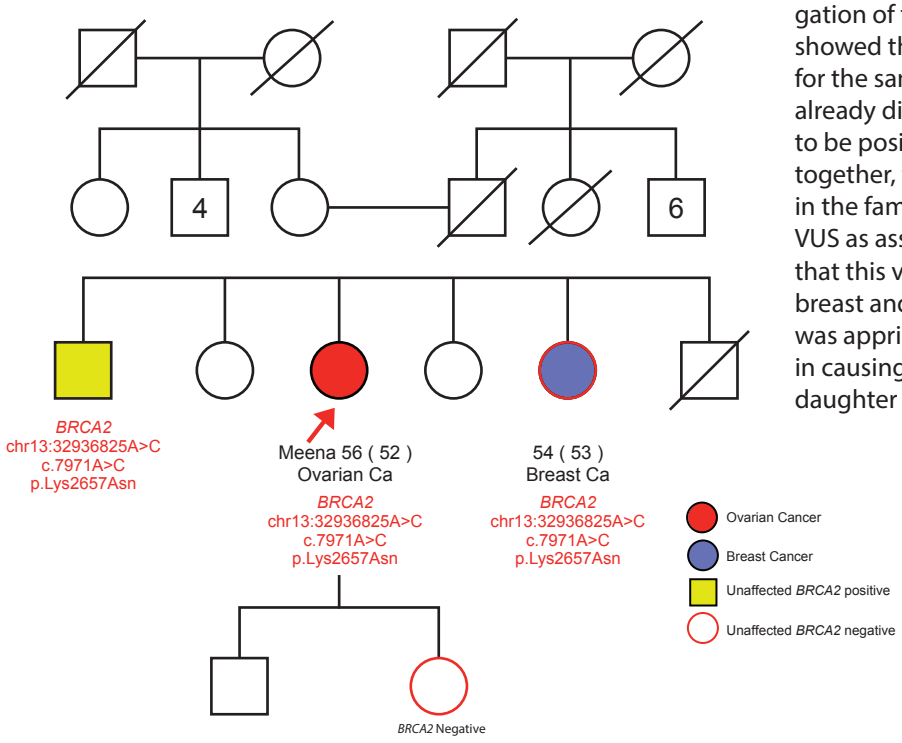
Key Findings

Gene	Variation	Zygosity	Clinical significance
BRCA2	chr13:32936825A>C c.7971A>C p.Lys2657Asn	Heterozygous	Variant of unknown significance

Variant description: The identified heterozygous missense substitution (p.Lys2657Asn) alters a conserved residue in the protein. The variant lies in the DNA binding domain (2470-3200 residues), which is involved in the physical interaction of *BRCA2* to both single-stranded DNA and double-stranded DNA. *In silico* missense prediction tools (SIFT, Mutation Taster, Polyphen-2, FATHMM, Mutation Assessor and Align-GVGD) suggest that this variant is probably damaging to protein function.

The identified mutation is classified as a 'Variant of Unknown Significance' or a VUS mutation. VUS mutations present a challenge for physicians since the evidence for the prescription of targeted therapies for such mutations is generally not available. In order to understand whether this mutation could possibly be harmful, Meena's siblings were advised to take the genetic test. If a VUS mutation shows co-segregation with disease phenotype in a family and is absent in healthy individuals, the mutation can be reconsidered as potentially pathogenic.

Family Tree- Post- test Genetic Counseling



Meena's family members were advised to take the *BRCA2* mutation specific test to understand co-segregation of this *BRCA2* mutation in the family. The results showed that Meena's brother was found to be positive for the same *BRCA2* mutation. Her sister who was already diagnosed with breast cancer was also found to be positive for the same *BRCA2* mutation. Taken together, the co-segregation with disease phenotype in the family as well as the deleterious impact of the VUS as assessed by *in silico* analytical tools indicate that this variant may be potentially pathogenic in breast and ovarian cancer. Hence, Meena's oncologist was apprised of the potential role of this VUS mutation in causing her ovarian cancer. Fortunately, Meena's daughter is negative for the *BRCA2* mutation.

Treatment Plan

Meena had been administered platinum-based chemotherapy for her ovarian cancer, but had relapsed, and finally was resistant to the chemotherapy. Following the identification of the *BRCA2* variant, she has been prescribed PARP inhibitor therapy[1–5], and is responding well to it.

Conclusion

- Additional analyses of VUS mutations can lead to identification of new, potentially pathogenic variants of *BRCA1* and *BRCA2* genes.
- The Strand Germline Cancer Test administered to multiple family members of breast and ovarian cancer patients helps to establish the risk of these cancers for the individuals tested.
- Genetic testing helped Meena receive PARP inhibitor therapy for ovarian cancer that was unresponsive to platinum-based chemotherapy.

References

1. *Oza, A. M. et al. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. Lancet Oncol. 16, 87–97 (2015).*

2. *Mirza, M. R. et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N. Engl. J. Med. 375, 2154–2164 (2016).*

3. *Swisher, E. M. et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. Lancet Oncol. 18, 75–87 (2017).*

4. *Crafton, S. M., Bixel, K. & Hays, J. L. PARP inhibition and gynecologic malignancies: A review of current literature and on-going trials. Gynecol. Oncol. 142, 588–596 (2016).*

5. *Jenner, Z. B., Sood, A. K. & Coleman, R. L. Evaluation of rucaparib and companion diagnostics in the PARP inhibitor landscape for recurrent ovarian cancer therapy. Futur. Oncol. 12, 1439–1456 (2016).*

Strand Germline Panel

The Strand Germline Cancer Test is designed to identify genes that are involved in several inherited cancers. The following genes are analyzed in samples from breast and ovarian cancer patients, as per international genetic testing guidelines.

ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, NBN, PALB2, PTEN, RAD51C, RAD51D, TP53

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