CASE STUDY

Mutation-Specific Testing: Eligibility for PARP Inhibitor Therapy Established

Gender: Female- Proband and Cousin sister (MST)

Age: Proband 44 years, MST patient- 48 years

Location: Jaipur, Rajasthan, & Mumbai, Maharashtra

Diagnosis: Ovarian Cancer in proband as well as in MST patient

Strand Test: Germline Cancer Test

Conclusion:

- Pathogenic mutation in *BRCA1* gene identified in proband
- Presence of same mutation in MST patient confirmed
- Eligibility of both women, for PARP inhibitor therapy, established
- Prevalence of HBOC in family confirmed
- Predictive risk assessment testing advised to extended family of proband, especially her children.

Introduction

Genetic testing is an emergent diagnostic technique that can provide specific and actionable inputs to the management of cancer therapy. Hereditary risk prediction for a predisposition towards breast and ovarian cancer is one of the significant benefits of genetic testing. The prevalence of hereditary breast and ovarian cancer (HBOC) in India is higher than that seen in other studies with subjects from the US and UK (Strand unpublished data).

Additionally, there are novel mutations in *BRCA1* and *BRCA2* genes prevalent in the Indian population (1). Prophylactic risk assessment of people whose relatives have developed breast and / or ovarian cancer is therefore highly important. Strand Life Sciences offers mutation-specific testing (MST), at nominal cost, to family members of patients in whom a pathogenic mutation has been identified by germline testing. In all such cases, it has led to accurate determination of personal risk of other family members, once a mutation in the index patient has been identified.

Patient Profile

Urmi Gehlot*, a 44-year-old IAS officer from Jaipur was diagnosed with ovarian cancer in 2012, when she was 41. Urmi consulted a prominent oncologist in Mumbai and was prescribed chemotherapy to treat her ovarian cancer. For the first three years, Urmi's cancer responded to platinum-based chemotherapy drugs but soon her symptoms of abdominal pain, fatigue, bloating and increase in abdominal girth recurred. Medical investigations confirmed that her cancer had indeed returned.

Since the cancer had developed resistance to platinum-based chemotherapy drugs, her oncologist advised her to undergo genetic counselling and genetic testing to understand if there was a hereditary mutation that was responsible for Urmi's ovarian cancer.

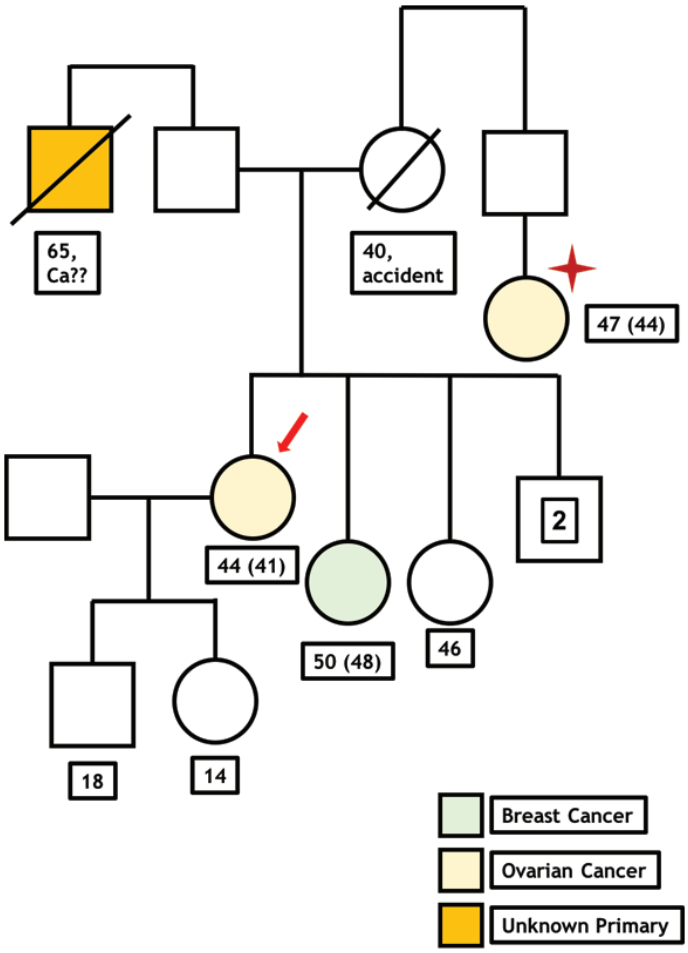
Family History

A genetic counsellor from Strand Life Sciences had a lengthy interaction with Urmi in order to understand whether there was a high occurrence of cancer in her first- and second-degree relatives. Urmi's sister had been diagnosed with breast cancer at the age of 48 years and was undergoing chemotherapy for the same.

Urmi's maternal cousin, Kritika*, had been diagnosed with ovarian cancer at the age of 44 years and was also undergoing chemotherapy (marked by the red '+' sign in the pedigree). Urmi's paternal uncle had also succumbed to cancer; however, the exact details of the primary cancer were not known to Urmi, at the time of counselling. Given the prevalence of breast as well as ovarian cancer in Urmi's sister and cousin, the Strand® Hereditary Cancer Test was advised to Urmi.

Name changed to protect patient privacy

Family Tree - Pre-Test Genetic Counselling



RESULT **Positive** for a heterozygous **'pathogenic'** variant, which was detected at the junction of exon 16-intron 16 of the *BRCA1* gene.

Key Findings

Gene	Variation	Zygosity	Clinical significance
BRCA1	chr17:41219624C>T c.5074+1G>A	Heterozygous	Pathogenic

Key Findings

- A pathogenic variant in the *BRCA1* gene was identified in Urmi's DNA.
- This mutation lies at the junction of exon16 and intron16 and is likely to cause a frameshift mutation in the mRNA.
- The resultant *BRCA1* protein is likely to be incomplete, leading to the loss of tumor suppression function.
- This genetic mutation is the most likely cause of Urmi's ovarian cancer.
- The same mutation has been identified in other Indian patients who also had other family members affected with breast and ovarian cancer.
- Individuals who are heterozygous for pathogenic variants in the *BRCA1* gene have a 50% chance of passing on the same gene to their children. Additionally, they are also at greater risk of developing pancreatic cancer (2,3).
- Urmi was advised about these potential health risks. Mutation-specific testing was advised to understand whether other family members, including her children, are also carriers of the same mutation or not.

Treatment Plan

Identification of the *BRCA1* mutation created new treatment options for Urmi. Her ovarian cancer was resistant to chemotherapy. However, the identification of the *BRCA1* mutation in her DNA, makes her eligible to receive PARP inhibitor therapy. Treatment of ovarian cancer patients with PARP inhibitors results in longer periods of progression-free survival in patients (4–8). PARP inhibitor therapy was also prescribed to another patient, Mrs. Meena Nandal, whose *BRCA2* mutation status was confirmed by germline testing at Strand.

Mutation-Specific Testing of Urmi's Relatives

In the follow-up session with a genetic counsellor, Urmi was advised about her treatment options as well as the possibility of getting other relatives tested to understand their own *BRCA* status. Urmi's maternal cousin, Kritika had also been diagnosed with ovarian cancer, and was undergoing treatment for the same. Kritika opted to take the MST to understand whether she could also be eligible for PARP inhibitor therapy.

Results of Mutation-Specific Testing*

The *BRCA1* mutation identified in Urmi's genome was also identified in Kritika's genome (Figure 1, blue vertical band). This test therefore confirmed Kritika's eligibility for receiving PARP inhibitor therapy.

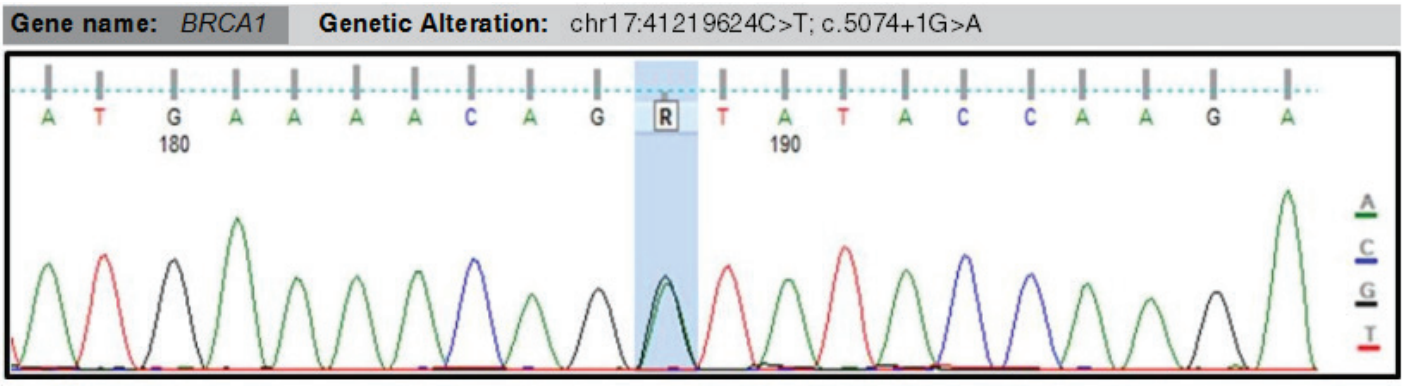


Figure 1: Sanger sequencing data (electropherogram) from the individual showing a heterozygous nucleotide change 'G>A' at position c.5074+1 in the *BRCA1* gene (RefSeq id: NM_007294). This variation was confirmed by sequencing with forward primer in two independent experiments.

The parameter marked with an * are not accredited by NABL and CAP.

Conclusions

- Urmi Gehlot, a 44-year-old woman from Mumbai was diagnosed with ovarian cancer and was advised genetic testing.
- Urmi's family history indicated a strong likelihood of hereditary breast and ovarian cancer in the family.
- The Strand® Hereditary Cancer Test facilitated the identification of a *BRCA1* founder mutation (*BRCA1* chr17:41219624C>T c.5074+1G>A) in the proband's DNA.
- Identification of this mutation indicates her eligibility to receive PARP inhibitor therapy instead of standard chemotherapy, for recurrent ovarian cancer.
- Mutation-specific testing was advised to Urmi's family members. Her cousin sister, Kritika, also diagnosed with ovarian cancer, opted to take the test.
- The same pathogenic *BRCA1* mutation was identified in Kritika's genome, making her eligible for PARP inhibitor therapy, as well.
- The presence of HBOC in the family was confirmed.
- Urmi and Kritika were advised about their risks for passing on the mutation to their progeny as well as the need for surveillance measures against pancreatic cancer.
- Mutation-specific testing of extended family members, once a pathogenic variant has been identified in a proband, can help to assess risk for hereditary cancer as well as support choice of targeted therapeutics.

Strand® Hereditary Cancer Test

The Strand Hereditary Cancer Test is designed to identify mutations in 19 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, EPCAM, MLH1, MSH2, MSH6, NBN, NF1, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53

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