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FOR GENOMICS & PERSONALIZED MEDICINE

CASE STUDY

Breast Cancer in Early Youth: Preventive Genetic Testing is Necessary

Gender: Female

Age: 30 years

Location: Mumbai

Diagnosis: Bilateral Breast Cancer

Strand Test: Germline Cancer Test

Conclusion: Eligibility for PARP inhibitor therapy established, *Ad hoc* genetic testing advisable

Patient Profile

Tamannah is a happily married young mother of two sons. Breast cancer was not a topic that was remotely connected with her life. At the age of 25, she was diagnosed with cancer of the right breast.

Tamannah was referred to a very well-known oncologist at a prominent hospital in Mumbai.

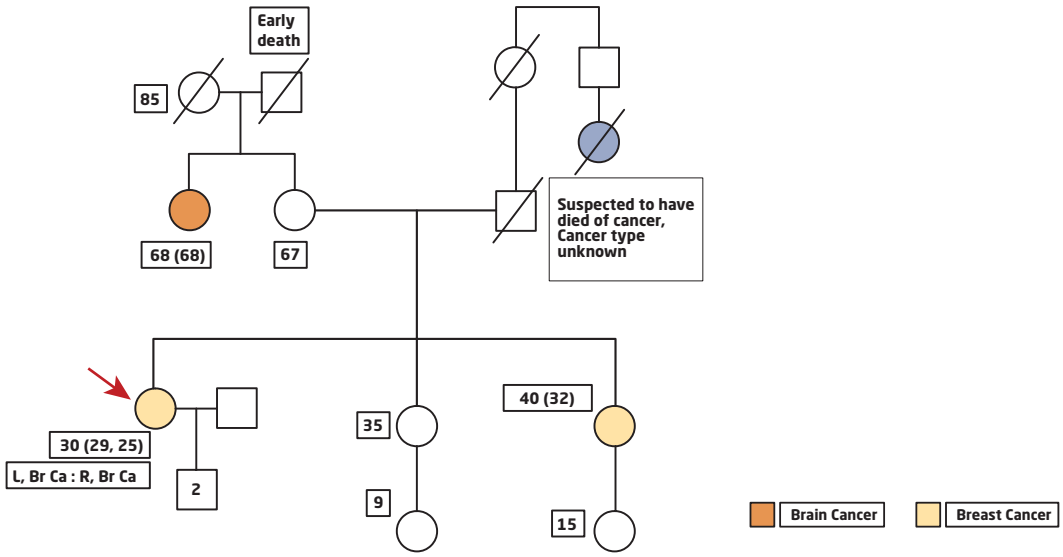
Initial Treatment

Tamannah underwent platinum-based chemotherapy for treatment of the cancer in her right breast. In the subsequent years, the disease seemed to remain under control. However, at the age of 29 years, Tamannah was diagnosed with contralateral breast cancer.

At this point, her oncologist advised her to undergo genetic testing to determine the genetic causes of her aggressive, early-onset breast cancer. Tamannah was referred to a genetic counselor from Strand Life Sciences to understand her pedigree. A good understanding of a person's family history is essential for a genetic counselor to estimate a person's risk for suffering from hereditary and familial cancers. This pre-test counseling also helps to choose the appropriate test from the Strand portfolio.

Family Tree – Pre-test Genetic Counselling

Tamannah has two other siblings (sisters). One of the sister was diagnosed with breast cancer at the age of 32 years. Their maternal aunt (mother's sister) had died of brain cancer at the age of 68 years. A deeper enquiry into the family history showed that Tamannah's maternal grand uncle's daughter had also died of cancer. However, the type of cancer could not be ascertained in this case.



*Name changed to protect patient privacy

Genetic Testing

Tamannah was advised to take the Strand Germline Cancer Test based on the fact that she and her sister were diagnosed with breast cancer at a young age as well as the prevalence of cancer in the maternal side of her family.

RESULT 

Positive for a heterozygous **'pathogenic' (disease-causing)** variant, which was detected in exon 2 of the *BRCA1* gene.

Key Findings

Gene	Variation	Zygosity	Clinical significance
BRCA1	chr17:41276045_41276046delCT c.68_69delAG p.Glu23ValfsTer17	Heterozygous	Pathogenic

The results showed that Tamannah was heterozygous for a pathogenic mutation in the *BRCA1* gene.

Treatment Plan

Tamannah had been prescribed chemotherapy for her bilateral breast cancer.

One of the targeted therapies developed for treatment of ovarian cancer patients who have mutations in *BRCA1* and *BRCA2* genes is a class of drugs that can stop the activity of an enzyme called poly-ADP-ribose polymerase, or PARP for short. PARP is an enzyme engaged in the repair of breaks in double stranded DNA. So, inhibition of this enzyme can actually promote the action of chemotherapy drugs that induce damage by breaking DNA strands, in actively growing cancer cells. PARP inhibitors have been approved for use in ovarian cancer patients bearing *BRCA1* and *BRCA2* mutations (Jenner et al. 2016; Crafton et al. 2016; Swisher et al. 2017; Mirza et al. 2016; Oza et al. 2015). PARP inhibitors are also thought to be effective in prostate cancer cells where stimulation of androgen- receptor mediated signalling leads to reduced expression of *BRCA1&2* genes, thereby creating conditions that mimic the presence of *BRCA1&2* mutations (also termed as **'BRCAness'** of tumor cells)(Li et al. 2017).

There is some evidence for a combinatorial use of inhibitors of *PI3K* and PARP, for the treatment of breast and ovarian cancer (Condorelli & André 2017). Evidence from pre-clinical trials and some phase II trials suggests that PARP inhibitors may be effective in treating breast cancer patients bearing germline *BRCA1* and mutations, despite receiving prior chemotherapy as well (Robert et al. 2017). Preliminary results from clinical trials of PARP inhibitors for treatment of breast cancer patients with *BRCA1* and *BRCA2* mutations have shown better progression-free survival than that seen with chemotherapy (Nicholas C. Turner, Melinda L. Telli, Hope S. Rugo, Audrey Mailliez, Johannes Ettl, Eva-Maria Grischke, Lida A. Mina, Judith Balmana Gelpi, Peter A. Fasching, Sara A. Hurvitz, Andrew M. Wardley, Colombe Chappey, Wendy Verret, Alison L. Hannah 2017; Robson et al. 2017; Mark E. Robson, Seock-Ah Im, Elżbieta Senkus, Binghe Xu, Susan M. Domchek, Norikazu Masuda, Suzette Delaloge, Wei Li, Nadine M. Tung, Anne Armstrong, Wenting Wu, Carsten Dietrich Goessl, Sarah Runswick 2017). Results from other ongoing phase III trials of PARP inhibitors for the treatment of breast cancer are still awaited.

The clinical application of PARP inhibitors is yet to receive FDA approval. However, in Tamannah's case, her eligibility to receive this targeted therapy, once approved in the future, has been established by genetic testing. She was also advised regarding prophylactic salpingo-oophorectomy to reduce her risk of suffering from ovarian cancer as well.

Conclusions

- Genetic testing established that Tamannah's breast cancer is hereditary in nature.
- The presence of a *BRCA1* mutation in her genome makes her eligible for PARP inhibitor therapy for her recurrent breast cancer, once the therapy receives FDA approval.
- Her elder sister's case should potentially have been considered as the index case for genetic counselling.
- The proband's family members have now been alerted to the presence of the hereditary *BRCA1* mutation and the enhanced likelihood of developing cancer. This awareness is likely to help them create a health surveillance plan and possibly take advantage of risk reduction mastectomy (RRM) and risk reduction salpingo-oophorectomy (RRSO), at an appropriate stage of life. Tamannah's children will also have the opportunity to undergo genetic counselling and testing when they reach adulthood.
- Early genetic testing for inheritance of germline *BRCA1 & BRCA2* mutations should be advised to identify high-risk patients like Tamannah, as a preventive measure. Periodic surveillance measures can then be put in place to diagnose breast cancer at the earliest possible stages.

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