CASE STUDY

Hereditary Breast and Ovarian Cancer: Not Just a *BRCA1 & 2* Playground

Gender: Female

Diagnosis: Cervical Cancer at 45 years, Breast Cancer at 59 years

Key Findings:

- Incidence of Lynch syndrome in the family.
- Multi-gene testing for hereditary breast and ovarian cancer is essential.
- Proband's children and siblings alerted to the presence of heritable mutation in the family.

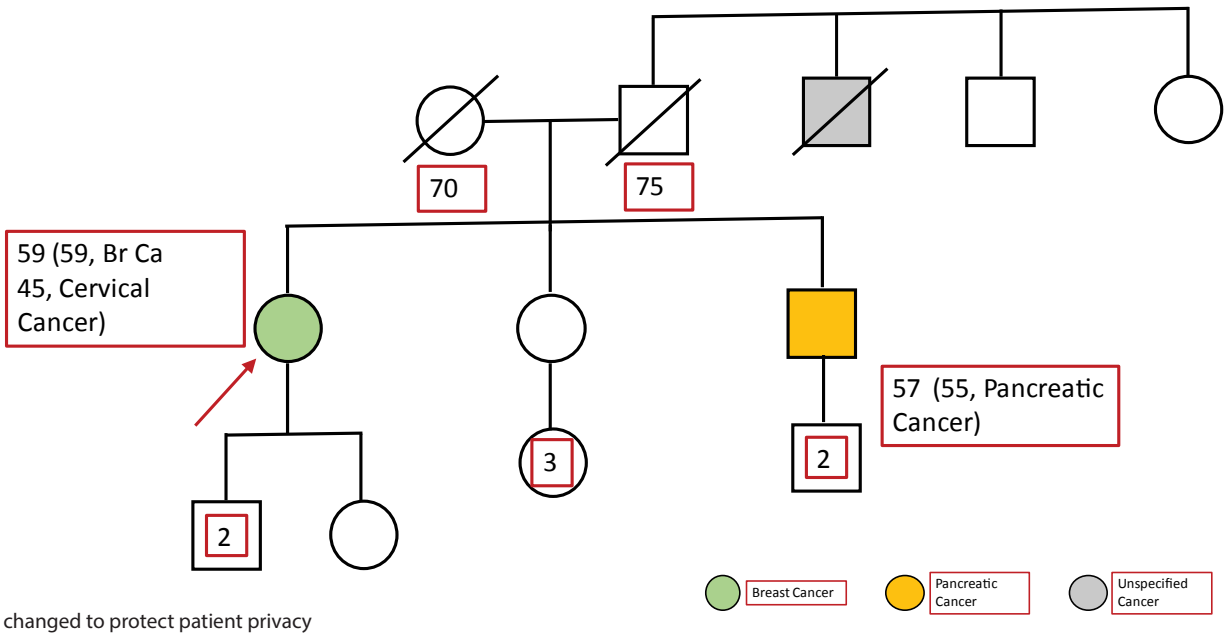
Patient Profile

Ameeta Srivastava* had come to terms with the fact that she had been diagnosed with cervical cancer at the age of 45 years. Cancer treatment was tough but she had survived it and gained some control over her health and life. Fate, or perhaps her own genes, however, had more surprises in store for her. Ameeta consulted a leading oncologist at a prominent hospital in Delhi, at the age of 59 years for pain in her breasts. She was diagnosed with breast cancer, her second encounter with cancer. The incidence of multiple cancers in the same person is definitely a red flag for the presence of inherited genetic mutations.

Cervical cancer is predominantly caused by infection with the human papillomavirus (HPV). However, genetic mutations in human proteins that interact with viral proteins can increase susceptibility towards multiple cancers, cervical cancer being one of them (Kutikhin & Yuzhalin 2012). Also, a case of a cervical tumor resulting from the presence of Lynch Syndrome in a young woman has been reported (Yousef et al. 2014). Additionally, patients suffering from Peutz-Jeghers syndrome, resulting from mutations in *STK11* gene, have been shown to be at a high risk for pancreatic and cervical cancer (Resta et al. 2013). Incidentally, breast cancer can also be a manifestation of Puetz-Jeghers syndrome (Song et al. 2006; Tchekmedyian et al. 2013). Considering these possibilities, Ameeta's oncologist advised her to undergo genetic testing.

Family Tree- Pre-Test Genetic Counselling

Considering her status as a cervical cancer survivor and the current incidence of breast cancer, her oncologist advised her to undergo genetic counselling. This was done to understand her family history and choose an appropriate genetic test- Germline or Somatic- in order to decide upon therapy options for her. Ameeta's brother had been diagnosed with pancreatic cancer at the age of 55 years. Her paternal uncle had also suffered from cancer although the family was not able to specify the type of cancer.



*Name changed to protect patient privacy

Results of Genetic Testing

The Strand Germline Cancer Test was advised to Ameeta, based on the incidence of multiple cancers in herself as well as pancreatic cancer in her first-degree relative. The Strand Germline Cancer test for hereditary breast and ovarian cancer is designed to identify mutations in 19 genes that can potentially be pathogenic. This comprehensive coverage includes high risk genes for hereditary cancer syndromes like Lynch, Li-Fraumeni, Cowden and Peutz-Jeghers syndrome in addition to *BRCA1*, *BRCA2* and *TP53*.

RESULT 

Positive for a heterozygous **'pathogenic'** variant which was detected in exon 16 of the *MLH1* gene.

Key Findings

Gene	Variation	Zygosity	Clinical significance
MLH1	chr3:37089130_37089132delAAG c.1852_1854delAAG p.Lys618del	Heterozygous	Pathogenic

Ameeta was found to be heterozygous for a pathogenic variant of the *MLH1* gene. She has a deletion mutation in the exon 16 of this gene.

Key Interpretations

- Ameeta has a single copy of a pathogenic variant of the *MLH1* gene that is associated with Lynch Syndrome predisposition. Germline pathogenic variations in the *MLH1* and *MSH2* genes account for about 90% of Lynch syndrome cases.
- The *MLH1* gene is required for corrections of mismatched base pairs during DNA synthesis.
- Mutations associated with Lynch syndrome can be inherited in an autosomal dominant manner. Therefore, having a single copy of the pathogenic variant increases the risk of getting cancer.
- The identified variant has been previously reported in a patient affected with breast cancer from a Danish Lynch syndrome cohort and the variant has been classified as 'pathogenic' (Jensen et al. 2010). In another study on a Danish Lynch syndrome cohort, the identified variant has been reported as a frequently occurring pathogenic variant (Nilbert et al. 2009).
- Manifestation of Lynch Syndrome as breast and ovarian cancer has been noted in studies with Asian patients as well (Wong et al. 2016).

Treatment Options

Ameeta was provided chemotherapy for her breast cancer. Recently, the US FDA has granted accelerated approval for the use of pembrolizumab for the treatment of solid tumors resulting from mutations of genes involved in the DNA mismatch repair (dMMR) pathway (https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm560040.htm). Lynch syndrome is a manifestation of mutations in genes in the same pathway. Therefore, Ameeta's physician can prescribe this drug to her, at his discretion.

Conclusions

- Ameeta's personal history of breast cancer could be due to the mutation in the *MLH1* gene which is involved in the DNA mismatch repair process.
- Ameeta's family has now been alerted to the presence of this inheritable pathogenic mutation in their genomes. Her sister, sister's children, as well as Ameeta's children should be tested for this particular mutation to understand their own risks for developing cancer.
- Multi-gene tests, such as the Strand Germline Cancer Test, that include genes other than *BRCA1, BRCA2* and *TP53* are useful in identifying syndromes like Lynch syndrome that may also manifest breast and ovarian cancer, in addition to colorectal cancers.
- Mutations in *MLH1* can increase a person's risk for developing colon cancer as well as endometrial cancer (Jasperson et al. 2010). Ameeta was counselled regarding surveillance and risk reduction measures against these tumors, as per NCCN guidelines.

Strand Germline Cancer Test

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, EPCAM, MLH1, MSH2, MSH6, NBN, NF1, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53

Other genes that were tested for incidental finding in this case are:
APC, BMPR1A, MEN1, MUTYH, NF2, RB1, RET, SDHAF2, SDHB, SDHC, SDHD, SMAD4, TSC1, TSC2, VHL, WT1

References

Jasperson, K.W. et al., 2010. Hereditary and familial colon cancer. Gastroenterology, 138(6), pp.2044–58. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20420945 [Accessed June 20, 2017].

Jensen, U.B. et al., 2010. Mismatch repair defective breast cancer in the hereditary nonpolyposis colorectal cancer syndrome. Breast Cancer Research and Treatment, 120(3), pp.777–782. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19575290 [Accessed May 8, 2017].

Kutikhin, A.G. & Yuzhalin, A.E., 2012. Inherited variation in pattern recognition receptors and cancer: dangerous liaisons? Cancer management and research, 4, pp.31–8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22427729 [Accessed June 20, 2017].

Nilbert, M. et al., 2009. Major contribution from recurrent alterations and MSH6 mutations in the Danish Lynch syndrome population. Familial Cancer, 8(1), pp.75–83. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18566915 [Accessed May 8, 2017].

Resta, N. et al., 2013. Cancer risk associated with STK11/LKB1 germline mutations in Peutz-Jeghers syndrome patients: Results of an Italian multicenter study. Digestive and Liver Disease, 45(7), pp.606–611. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23415580 [Accessed June 20, 2017].

Song, S.-H. et al., 2006. Peutz-Jeghers Syndrome with multiple genital tract tumors and breast cancer: a case report with a review of literatures. Journal of Korean medical science, 21(4), pp.752–7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16891826 [Accessed June 20, 2017].

Tchekmedyian, A. et al., 2013. Findings from the Peutz-Jeghers syndrome registry of uruguay. PloS one, 8(11), p.e79639. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24260271 [Accessed June 20, 2017].

Wong, E.S.Y. et al., 2016. Inherited breast cancer predisposition in Asians: multigene panel testing outcomes from Singapore. npj Genomic Medicine, 1, p.15003. Available at: http://www.nature.com/articles/npjgenmed20153 [Accessed December 6, 2016].

Yousef, I. et al., 2014. Cervical neuroendocrine tumor in a young female with Lynch Syndrome. Neuro endocrinology letters, 35(2), pp.89–94. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24878972 [Accessed June 20, 2017]. https://www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf

Strand Center for Genomics & Personalized Medicine
(A unit of Strand Life Sciences Pvt. Ltd.)
UAS Alumni Association Building, Veterinary College Campus,
Bellary Road, Hebbal, Bangalore – 560 024
Phone: 1800-1022-695, support.strandx@strandls.com, www.strandls.com

Strand Center for Genomics & Personalized Medicine is accredited by

CAP ACCREDITED # 8750941

Certificate No. M-0849

#StayAheadOfCancer

Strand ID: GL521824052017