Executive Summary:

Germline TP53 variant of uncertain significance (VUS) in a 47-year-old ESCC patient, Madhuri Gaur, who succumbed to the disease on 17th December 2023 after an early onset diagnosis at the age of 44, leaving behind 3 student sons (21 years, 20 years, and 14 years old) and a graduate daughter (25 years old). Three children who have been tested also carry this variant (25-year-old Radhika Gaur, 21-year-old Mohit Gaur and 20-year-old Rohit Gaur). As per the report, C.266C>A (p.Pro91His) Variant is a missense type with heterozygous zygosity. SIFT and various other bioinformatics tools predict a damaging nature. The reference codon is conserved in mammals. The variant has a combined phenotype score of -0.315 ± 0.059, and transcriptional activity in yeast is 5.96%. Mutation probability (COSMIC Signature 1 percentile) is 65.33%. The variant is extremely rare and has not been found in 1000 genomes, gnomAD, IARC, ExAC, and MedGenome’s internal databases. A paper on PubMed shows that one HBOC patient who is not a part of this family also had this variant. Madhuri Gaur was 3rd in her bloodline to have cancer (a 60-year-old maternal uncle of Madhuri Gaur has a uvular lesion of moderately differentiated squamous cell carcinoma, and the histopathological details for the other cancer case of a 45-year-old maternal uncle are not available), and she developed cancer for the third time after achieving pathological complete response twice. Additionally, excluding the 3 previously mentioned cancer cases including the patient, 3 of her siblings died as children without a diagnosis of any specific ailment and further familial medical history is unavailable.

  Questions:

1. What's the plan now?

2. I don't want to live forever, but I have long-term goals. Give me an honest idea about my future so I can modify my goals accordingly.

3. Where can I get functional studies done for this variant?

4. How can we get a comparative analysis done with other variants?

5. Who is the best person to help me with segregation analysis?

6. Who can help me calculate the mathematical probability of developing some form of malignancy due to this variant?

7. Can you tell me more about this variant using the data provided by me? Do you have any other data about this variant? Can you please help me understand this data during my next visit, especially data taken from PHANTM and TP53 database?

8. What research options can be explored?