

## CASE STUDY

# Germline Cancer Testing in A Proband: Extension of Benefits to Unaffected Family Members

### Introduction

Most cancers are caused by genetic damage resulting from random mutations and exposure to cancer-causing substances. However, a small percentage of cancers are caused by inherited mutations that are passed on from generation-to-generation.

Typically, individuals who have a defective cancer-causing gene, are prone to suffer from cancer at an early age, and are also likely to have primary cancers in one or more organs, eg. breast and colon. Incidence of cancer at a young age poses significant financial and socioeconomic challenges.

Hereditary Breast and Ovarian Cancer (HBOC) syndrome, Peutz-Jeghers syndrome, Lynch syndrome, Cowden syndrome are some examples of hereditary cancer syndromes. Genetic tests are available to understand the mutation status of 19 genes that are associated with some of the well-known hereditary cancer syndromes. The unique utility of this test (called the Germline Cancer Test) is that it can be used for people with a confirmed incidence of cancer to understand whether their cancer is familial or sporadic cancer.

Additionally, the test can be used by normal (unaffected) individuals in a pre-emptive mode, in order to understand their personal risk for developing cancers. Risk management strategies can be brought into practice to identify symptoms of cancer in the early stages.

### Patient Profile

Sohanlal Shah\*, aged 52 years, had a thriving spice trade in Ahmedabad. He had a busy work life, but physical activity coupled with a sensible vegetarian diet helped him maintain a healthy lifestyle.

His family members had been diagnosed with various kinds of cancers, and sometimes he wondered whether more bad news was in store for him. When he started having symptoms of pain during bowel movements and frequent episodes of diarrhea, he consulted his primary care physician. In turn his physician directed him to consult Dr. Shirish Alurkar, a renowned oncologist in Ahmedabad.

### Family History

Clinical investigations revealed that Sohanlal was suffering from colorectal cancer. A preliminary enquiry into the incidence of cancers in Sohanlal's family suggested that the family may be carrying a hereditary mutation. Hence, Dr. Alurkar suggested a counselling session with a genetic counselor from Strand, in order to understand the family history in detail.

A genetic counselor is trained to understand inheritance patterns of genes and suggest the choice of a Germline or a Somatic test for genetic analysis. A pedigree chart was constructed to capture the incidence of cancer in Sohanlal's family.



**Gender:** Male

**Age:** 52 years

**Location:** Ahmedabad, Gujarat

**Diagnosis:** Lynch Syndrome

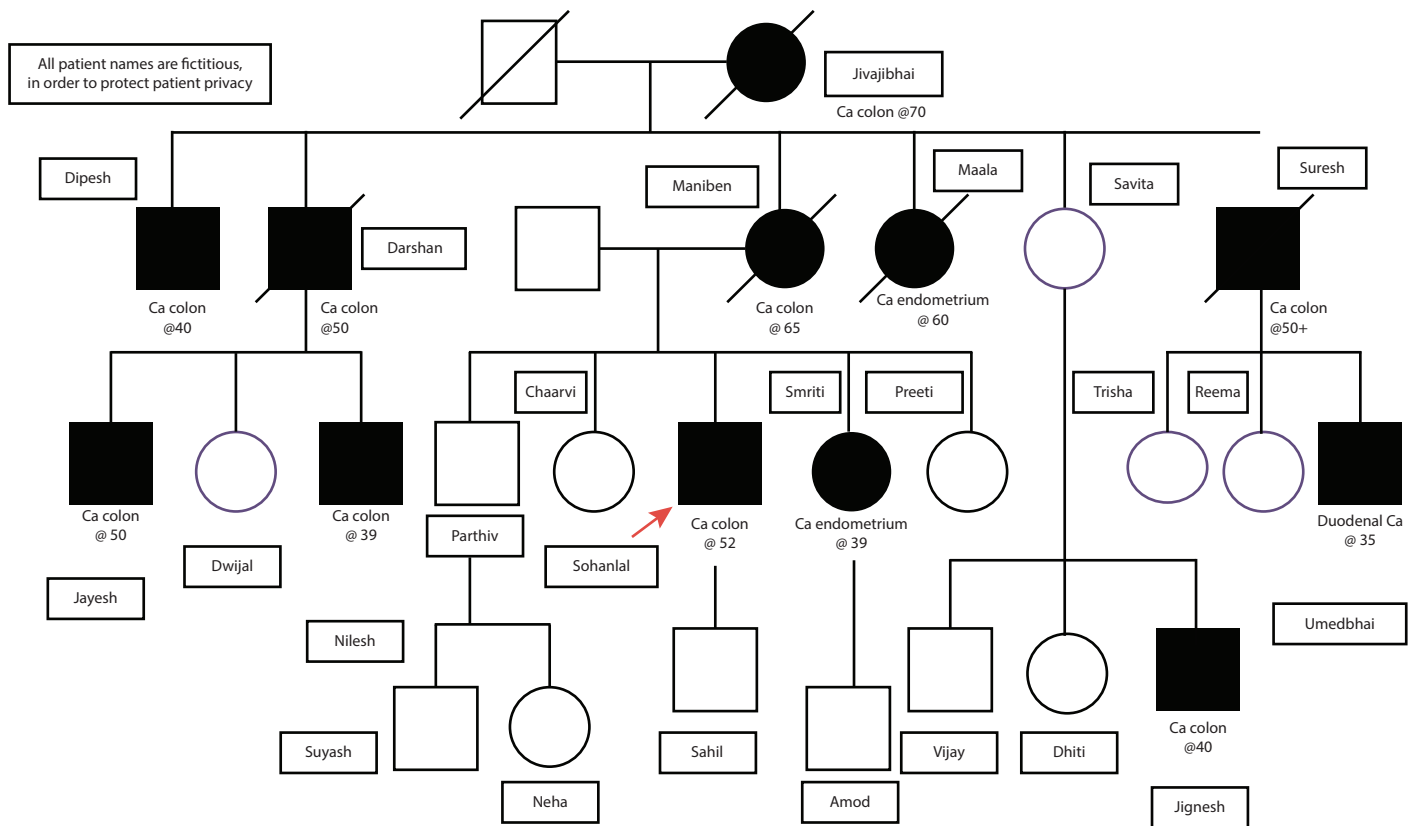
**Strand Test:** Germline Cancer Test

#### Conclusion:

- Likely pathogenic mutation in the *MLH1* gene identified
- Incidence of Lynch syndrome in family confirmed
- Mutation-specific test used by 7 family members – 5 tested negative, 2 tested positive but unaffected by cancer at the time of testing
- Surveillance measures adopted by the 2 positive individuals

\*Name changed to protect patient privacy

## Family Tree - Pre-Test Genetic Counselling



Sohanlal has 3 sisters and a brother. One of his sisters, Smriti, had been diagnosed with endometrial cancer at the age of 39 years. Their mother, Maniben, has been diagnosed with colorectal cancer when she was 65 years old and had succumbed to the disease. Her sister (Maala, Sohanlal's maternal aunt) had lost her life to endometrial cancer at the age of 60 years.

Sohanlal has three maternal uncles and all had been diagnosed with colorectal cancer at 40 years (Dipesh), 50 years (Darshan), and 50+ years (Suresh) of age, respectively. Darshan, deceased due to colorectal cancer, had two sons and a daughter and both the sons, Jayesh and Nilesch had been diagnosed with colorectal cancer, at the ages of 50 and 39 years, respectively.

Sohanlal's cousin, Umedbhai (Suresh's son) had been diagnosed with duodenal cancer at the age of 35 years. Another cousin, Jignesh was also battling colorectal cancer. All in all, 7 family members have been battling cancer at the time of Sohanlal's diagnosis.

Going further into the earlier generation, Sohanlal's grandfather Jivajibhai had lost his life to colorectal cancer at the age of 70 years.

Given the high prevalence of colon cancer as well as endometrial cancer in the family, a diagnosis of 'hereditary non-polyposis colorectal cancer' was suspected. The Strand Germline test was prescribed to Sohanlal to understand if hereditary mutations were present in his genome.

## Results of Genetic Testing

A 'likely pathogenic' variant of the *MLH1* gene- a deletion in exon 2- was identified in Sohanlal's genome. Sohanlal is heterozygous (carries one copy) for this mutation. However, since mutations in *MLH1* are inherited in an autosomal dominant manner, one mutant copy is sufficient to cause colorectal cancer (Kohlmann & Gruber, 1993).

### RESULT



A 'likely pathogenic' variant in exon 2 of the *MLH1* gene was identified.

### Key Findings

Gene	Variation	Zygoty	Clinical significance
<i>MLH1</i>	chr3:37038149delA c.156delA p.Glu53ArgfsTer4	Heterozygous	Likely Pathogenic

### Key Findings

- ◆ A mutation in exon 2 of the *MLH1* gene was identified in Sohanlal's genome
- ◆ The identified heterozygous deletion (c.156delA) will cause a frameshift leading to premature termination of the protein (p.Glu53ArgfsTer4).
- ◆ The truncated protein is predicted to have a length of 56 amino acids (aa) as opposed to the original length of 756 aa.
- ◆ The truncated protein is likely to lack the functionally important ATPase domain, the MutS interaction domain as well as the PMS2/MLH3/PMS1 interaction domain of MLH1 protein, which will likely cause loss-of-function.
- ◆ The identified variant is in the vicinity of several other variants that have been known to be associated with Lynch Syndrome.
- ◆ Hence, the variant has been classified as a 'Likely Pathogenic' variant.
- ◆ The proband was advised about the chances of passing on this mutation to his son, Sahil.
- ◆ Mutation-specific testing was offered to the immediate relatives of the proband to understand their status.

### Mutation- Specific Testing\*

A mutation-specific test (MST) is a test designed to assess the presence or absence of specific mutations within a proband's genome. This test was offered to other family members, Parthiv, Chaarvi, Sahil, Amod and Preeti, in 2015, in order to determine whether they had inherited the same mutation or not. Sohanlal's siblings, Parthiv, Chaarvi and Preeti were negative for the *MLH1* mutation. Sohanlal's son, Sahil and nephew Amod were positive for the *MLH1* mutation and were unaffected by cancer at the time of testing.

In 2017, Suyash and Neha (Parthiv's children) wanted to understand their personal risk for cancer, despite the fact that their father was negative for the tested mutation, and took the same MST as their cousins.

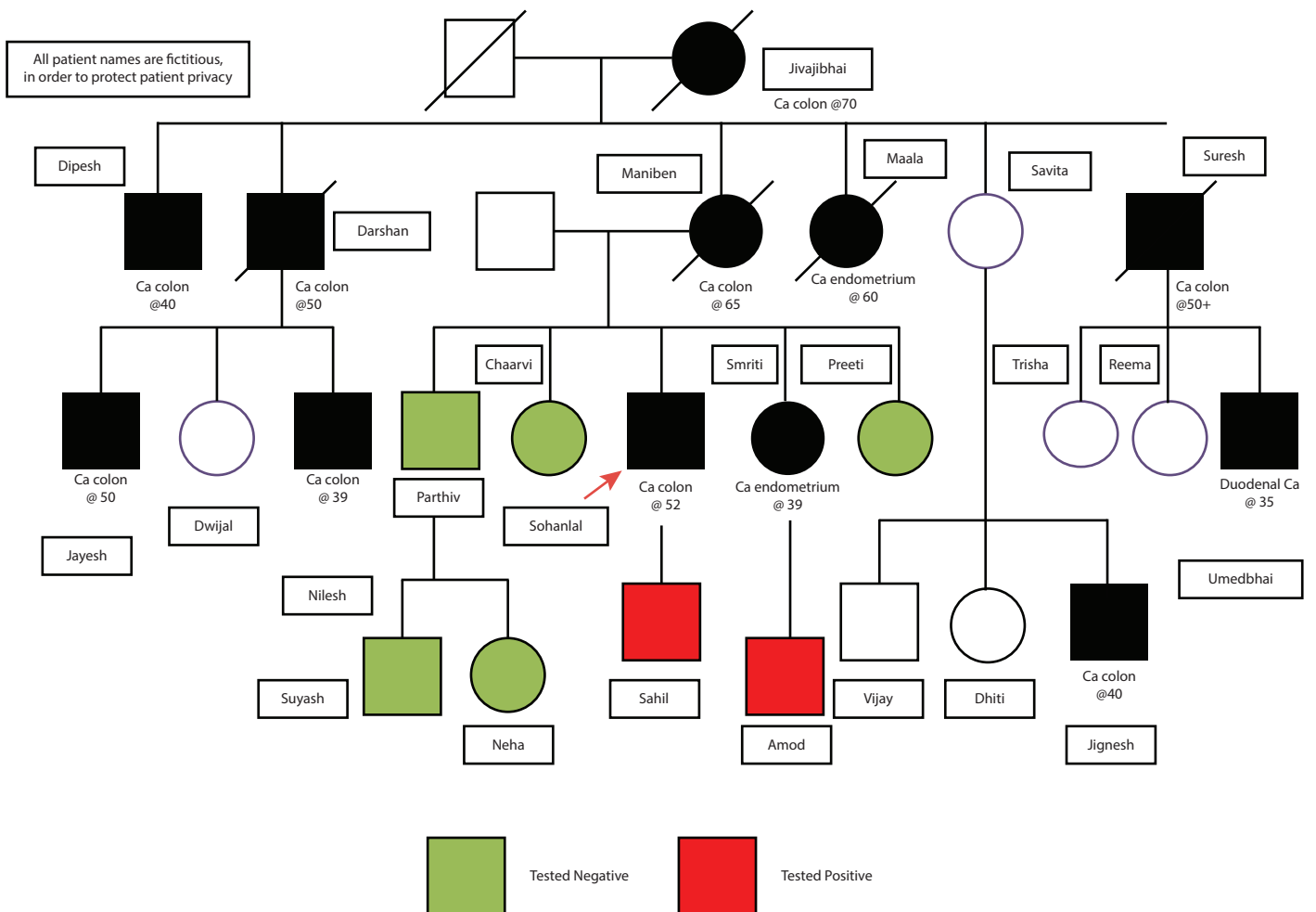
The parameter marked with an \* are not accredited by NABL and CAP.

## Results of Mutation-Specific Testing (c.156delA p.Glu53ArgfsTer4, RefSeq ID: NM\_000249)

Family Member	Health status	Genetic Status	Year
Preeti	Unaffected by cancer	Negative for the <i>MLH1</i> mutation	2015
Charvi	Unaffected by cancer	Negative for the <i>MLH1</i> mutation	2015
Parthiv	Unaffected by cancer	Negative for the <i>MLH1</i> mutation	2015
Sahil	Unaffected by cancer	Positive for the <i>MLH1</i> mutation	2015
Amod	Unaffected by cancer	Positive for the <i>MLH1</i> mutation	2015
Suyash	Unaffected by cancer	Negative for the <i>MLH1</i> mutation	2017
Neha	Unaffected by cancer	Negative for the <i>MLH1</i> mutation	2017

Table 1. Results of Mutation-Specific Testing in Proband's Extended Family

### Family Tree Post Genetic Testing



## Surveillance Measures Against Cancer

A positive identification of a pathogenic or likely pathogenic germline mutation in a person's DNA can be used as a preparatory signal for increased surveillance against cancer. Sahil and Amod were unaffected by cancer at the time of testing. They were advised about their risks for developing various types of cancers and were provided with the following guidelines by NCCN, to take care of their health. Adoption of these surveillance measures can help to spot the signs of cancer at the very earliest, thereby increasing their chances of having many therapeutic options, including surgical removal in the early stages.

Type of Cancer	Surveillance and Management Strategies
Colon Cancer	Colonoscopy every 1-2 years starting from age 20-25, or 2 to 5 years before the earliest age of diagnosis of colorectal cancer in the family Annual colonoscopy after the age of 40 years.
Endometrial and Ovarian Cancers	Gynecologic exam, transvaginal ultrasound, endometrial aspiration and CA-125 test every year, beginning between age 25-35 years
Gastric and Duodenal Cancers	Upper gastro-intestinal endoscopy and extended duodenoscopy at age 25-30 years. Follow-up every 1-3 years based on findings
Other Lynch Syndrome -related cancers	Urothelial cancer: Annual urine analysis for signs of cancer Central Nervous System Cancer: Annual physical examination

Table 2. Health Surveillance Advice for Carriers of *MLH1* Germline Mutations

## Key Findings

- ◆ Sohanlal, a 52-year-old man from Ahmedabad was diagnosed with colorectal cancer and was advised genetic testing.
- ◆ Sohanlal's family history indicated a strong likelihood of hereditary non-polyposis colorectal cancer (Lynch Syndrome) in the family.
- ◆ The Strand Germline Cancer Test facilitated the identification of an *MLH1* mutation in the patient's DNA.
- ◆ The mutation is in the vicinity of other known pathogenic mutations in the *MLH1* gene. Considering the location and the predicted effect on the produced protein, this mutation was classified as a 'likely pathogenic' one.
- ◆ Mutation-specific testing of seven other family members led to the identification of two members who have inherited the same pathogenic mutation but were unaffected at the time of testing. Five other relatives of the proband have tested negative for this germline mutation.
- ◆ Proband's son and nephew who are heterozygous carriers of this germline mutation have been advised to adopt surveillance measures to spot the earliest signs of cancer.
- ◆ Germline cancer tests can be leveraged for pre-emptive care and to actually reduce one's personal risk for cancer considerably.

## Strand Germline Cancer Test

The Strand Germline Cancer Test is a Laboratory Developed Test (LDT) that has been developed and its performance characteristics determined by Strand Center for Genomics and Personalized Medicine at Strand Life Sciences.

This test covers 19 genes:

*ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, NBN, NF1, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53*

## References

Kohlmann, W., & Gruber, S. B. (1993). Lynch Syndrome. GeneReviews®. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/20301390>



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