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"Low/Moderate Penetrance" *APC* Gene Mutation c.3920T>A (I1307K)

Mutations or changes in the *APC* gene are typically associated with a severe genetic condition known as Familial Adenomatous Polyposis syndrome or FAP. Individuals with FAP develop 100s to 1000s of colon polyps in their lifetime and have almost a 100% risk to develop colon cancer without intervention. However, the particular mutation found in the APC gene in **FNAME does NOT cause FAP and FNAME does NOT have this condition**

Risks and Management Recommendations

The mutation identified in FNAME (*APC* I1307K) is a well-known mutation and is found in approximately 10% of the Ashkenazi Jewish population. While it is known that individuals with this mutation do not have FAP, some literature suggests individuals with this mutation have a 1.5-1.9 fold relative risk to develop colon cancer.[1] The general population risk to develop colorectal cancer by age 80 is approximately 4.2%, thus a 1.5-1.9 fold risk is approximately a 6.3-8.0% risk to develop colorectal cancer by age 80. Other literature suggests there may be no increased risk for colorectal cancer in individuals with this variant[2], however no single study to date has been definitive. A 1.5-1.9 fold increased risk for colon cancer could be considered similar to the risk of developing colon cancer associated with having a first-degree relative (i.e., parent, sibling, child) affected with colon cancer under age 50.

The National Comprehensive Cancer Network (NCCN) publishes guidelines for the management of individuals and families with cancer predisposition syndromes. The NCCN Guidelines Version 3.2019 recommends the following surveillance for individuals with the *APC* I1307K mutation:

- For individuals unaffected by colorectal cancer: colonoscopy screening every 5 years, beginning at age 40 or 10 year prior to the earliest age of colorectal cancer diagnosis in a firstdegree relative (i.e., parent, sibling, child), whichever comes first.[3]
- For individuals with colorectal cancer: consult with physician to determine appropriate colon cancer risk management options.[3]

Implication for Family Members/Reproductive Considerations

- First-degree relatives (i.e., parents, siblings, and children) have a 50% chance to have the familial *APC* mutation. Second-degree relatives (i.e., nieces/nephews, aunts/uncles, and grandparents) have a 25% chance to have the familial mutation.
- For carriers of a known mutation, assisted reproduction (with or without egg or sperm donation), pre-implantation genetic testing, and prenatal diagnosis options exist.
- All family members are encouraged to pursue genetic counseling to clarify their risks. Family members may visit www.FindAGeneticCounselor.com to find genetic services near them.

References

1. Woodage, T., King, S., Wacholder, S. et al. The *APC* I1307K allele and cancer risk in a community-based study of Ashkenazi Jews. *Nat Genet* 20, 62–65 (1998). doi:10.1038/1722
2. Strul, H., Barenboim, E., Leshno, M. et al. The I307K Adenomatous Polyposis Coli gene does not contribute in the assessment of risk for colorectal cancer in Ashkenazi Jews. *Cancer Epidemiology, Biomarkers & Prevention* 12(10), 1012-1015 (2003).

3. National Comprehensive Cancer Network (NCCN). Genetic/Familial High-Risk Assessment: Colorectal (version 3.2019). *NCCN Clinical Practice Guidelines in Oncology* (2019).