THE IMPACT OF NCCN MANAGEMENT GUIDELINES ON APC I1307K CARRIERS UNAFFECTED WITH COLORECTAL CANCER

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**Background**

- Pathogenic variants in APC predispose to Familial Adenomatous Polyposis (FAP) and up to 100% risk of colorectal cancer (CRC) in untreated individuals.
- In contrast, APC c.3920T>A (I1307K) is a risk allele associated with an approximately 2-fold increased risk for CRC in individuals of Ashkenazi Jewish (AJ) ancestry.¹,²,⁵
- CRC risks in individuals of other ancestries are not well-elucidated in the literature.
- The National Comprehensive Cancer Network (NCCN) recently released Genetic/Familial High-Risk Assessment: Colorectal management guidelines (Version 1.2016), for unaffected APC I1307K carriers, regardless of ancestry, recommending colonoscopy every 5 years starting at age 40.⁴

**Methods**

- We retrospectively reviewed all clinical data provided on test request forms for individuals found to be heterozygous for APC I1307K via multi-gene hereditary cancer panel testing.
- Only individuals with no personal history of CRC were included in this analysis, as a personal history of CRC would alter future screening/management guidelines.
- Only 13/139 individuals with the risk allele had ordered a CRC-related panel, suggesting that CRC was not the main or only concern in the clinical history.
- For 5 women, the variant was identified on a reflex panel after a breast-specific or custom panel was negative.

**Results**

- 139 individuals reporting no personal history of CRC were heterozygous for APC I1307K.
- Only 13/139 individuals with the risk allele had ordered a CRC-related panel, suggesting that CRC was not the main or only concern in the clinical history.
- For 5 women, the variant was identified on a reflex panel after a breast-specific or custom panel was negative.

- 88.5% (123/139) of unaffected individuals, would have increased CRC screening recommendations solely based on the presence of APC I1307K.
- 31.7% (39/123) of those who would have increased CRC screening based on the presence of APC I1307K reported no AJ ancestry.
- 11.5% (16/139) of unaffected individuals, would not see a change in their screening recommendations based on the presence of APC I1307K, as they had significant family history that already warrants increased screening.
- 15 individuals had at least one first degree relative (FDR) with CRC diagnosed <60.
- One individual had two FDRs with CRC diagnosed < 60 (both parents).

**Conclusions**

- The majority of individuals without CRC in our cohort could be offered more intense colon cancer screening based solely on the presence of APC I1307K under the NCCN management guidelines.
- Further studies, including prospective tracking of unaffected individuals with APC I1307K, are needed to determine the benefits of increased CRC screening in this population, particularly in non-Ashkenazi Jewish individuals.

**References**