# Ancestry-Based Cancer Risks Associated with *APC* I1307K

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## BACKGROUND

- Individuals with pathogenic variants in *APC* have Familial/Attenuate Adenomatous Polyposis syndrome (FAP/AFAP). They may have a 70-99% lifetime risk for colorectal cancer.
- *APC* I1307K is a polymorphism that occurs in 10.1% of individuals of Ashkenazi Jewish (AJ) ancestry and does not cause FAP/AFAP.
- *APC* I1307K is associated with a slightly increased colorectal cancer risk among individuals of AJ ancestry that has not been found in other ancestries.
- The aim of this study was to evaluate ancestry-based cancer risks for *APC* I1307K carriers.

## METHODS

### *COHORT*

- We investigated individuals who underwent clinical genetic testing with a 25-gene hereditary cancer panel that includes *APC* between September 2013 and July 2016.
- Only individuals for whom panel testing was initially ordered were included here. This excludes individuals of AJ ancestry who were first tested for the 3 common founder mutations.
- Individuals were ascertained for testing based on clinical suspicion of hereditary cancer risk.

### *ANALYSIS*

- Individuals who were negative for pathogenic variants (PVs) other than *APC* I1307K were included in the analysis.
- The prevalence of *APC* I1307K was evaluated according to ancestry for individuals who reported:
  1. Full AJ ancestry (n=3,015)
  2. Partial AJ ancestry (n=2,054)
  3. No AJ ancestry (n=171,414)
- Individuals were excluded from analysis if no ancestry was indicated on the test request form.
- Personal cancer history was assessed in *APC* I1307K carriers relative to non-carriers.
- All clinical information was collected on the provider-completed test request form.

## RESULTS

***Figure 1. Ancestry of I1307K Carriers (N = 581)***

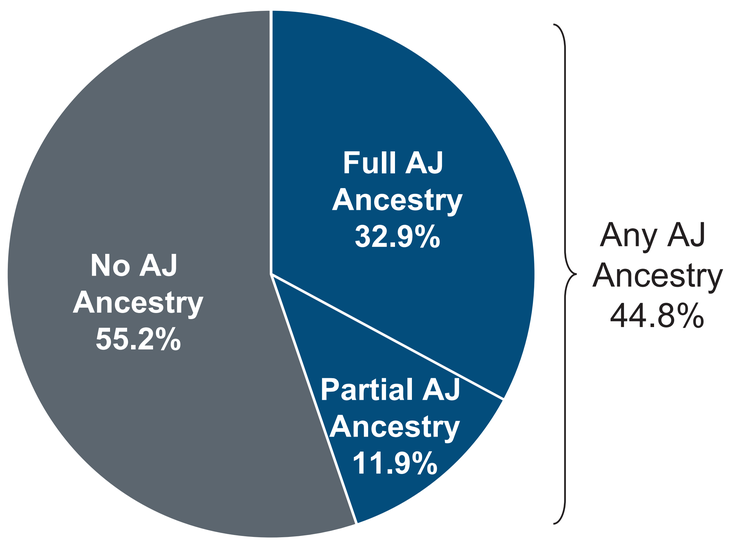
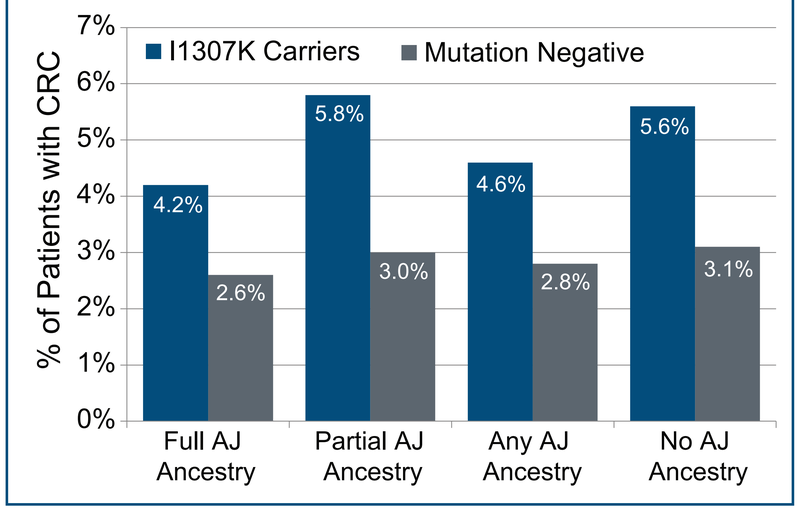



***Figure 2. Ancestry of Individuals with a Personal History of Colorectal Cancer***




- 581 *APC* I1307K carriers were identified (Fig. 1).
  - 191 (32.9%) reported full AJ ancestry and 69 (11.9%) reported partial AJ ancestry
- A higher proportion of individuals of full AJ ancestry (6.3%) were found to carry the *APC* I1307K variant relative to individuals of partial AJ (3.4%) or no AJ (0.2%) ancestry.
- There was a similar incidence of breast cancer among *APC* I1307K carriers and non-carriers for all ancestries (Table 1).
- *APC* I1307K carriers with full or partial AJ ancestry had a higher incidence of colorectal cancer relative to non-carriers (Table 1, Fig. 2).
  - When all AJ ancestry is combined (full or partial), this increased incidence of colorectal cancer is trending towards significance (p=0.087).
- *APC* I1307K carriers with no AJ ancestry had a statistically significant increase in colorectal cancer incidence relative to non-carriers (p=0.014) (Fig. 2).

***Table 1. Personal Cancer History***

| Cancer Type | *APC* I1307K Carriers | | | Mutation Negative | | |
|---|---|---|---|---|---|---|
| | Full AJ Ancestry (n = 191) | Partial AJ Ancestry (n = 69) | No AJ Ancestry (n = 321) | Full AJ Ancestry (n = 2,824) | Partial AJ Ancestry (n = 1,985) | No AJ Ancestry (n = 171,093) |
| Breast | 39 (20.4%) | 12 (17.4%) | 75 (23.4%) | 516 (18.3%) | 433 (21.8%) | 49053 (28.7%) |
| Colorectal | 8 (4.2%) | 4 (5.8%) | 18 (5.6%) | 74 (2.6%) | 60 (3.0%) | 5229 (3.1%) |
| 1-5 polyps | 9 (4.7%) | 1 (1.4%) | 7 (2.2%) | 64 (2.3%) | 56 (2.8%) | 2744 (1.6%) |
| >5 polyps | 5 (2.6%) | 6 (8.7%) | 6 (1.9%) | 40 (1.4%) | 25 (1.3%) | 1794 (1.0%) |

## CONCLUSIONS

- Our findings support previous studies that show an increased risk of colorectal cancer among *APC* I1307K carriers of AJ ancestry. In addition, our data suggests that there may be an increased risk of colorectal cancer among *APC* I1307K carriers of non-AJ ancestry.
- The increased incidence of colorectal cancer among individuals of AJ ancestry may not have reached statistical significance due to the exclusion of individuals who underwent founder mutation testing.
- Overall, the data presented here are in line with recent NCCN guidelines that recommend increased screening for *APC* I1307K carriers.

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