

Case Report

# Homozygous Germline APC p.I1307K Variants: A Case Series

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## Keywords

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## Abstract

Approximately 10% of all colorectal cancer is estimated to be due to an inherited predisposition. Identification of a germline pathogenic variant can aid in treatment, screening, and surveillance and help stratify familial cancer risks based on gene-specific cancer associations. The APC gene contributes to a small percentage of hereditary colon cancer, with most pathogenic APC variants causing familial adenomatous polyposis syndrome. However, one specific variant in APC called p.I1307K, found in approximately 10% of Ashkenazi Jewish individuals, is associated with a moderate risk for colon cancer, but not polyposis. Heterozygous carriers of one p.I1307K variant are well documented in the literature, and guidelines recommend earlier and more frequent colonoscopies. Conversely, reports of homozygous carriers of 2 p.I1307K variants are limited, and guidelines for medical management are lacking. This case series describes 4 homozygous p.I1307K patients of Ashkenazi Jewish ancestry identified in cancer genetics clinics. Case 1 is a 73-year-old pancreatic cancer patient with a family history of melanoma and colon cancer. Case 2 is a 62-year-old patient with a personal history of 4 adenomatous colorectal polyps and a family history of breast, pancreatic, colon, and prostate cancers. Case 3 is a 52-year-old patient with a personal history of early-onset breast cancer and uveal melanoma and a family history of breast, prostate, and stomach cancers. Case 4 is a 70-year-old patient with a personal history of gallbladder adenocarcinoma and a family history of breast cancer. These cases exhibit wide phenotypic variability and contribute to the limited reports of homozygous p.I1307K variant carriers.

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## Introduction

Colon cancer is the fourth leading cause of cancer and the second leading cause of mortality from cancer in the USA [1]. Of new colon cancer diagnoses, approximately 10% are due to inherited cancer syndromes [2]. While Lynch syndrome accounts for 3% of all inherited colorectal cancers, germline pathogenic variants in a variety of other cancer predisposition genes can be found in the remaining individuals who test positive [2]. Familial adenomatous polyposis, which accounts for close to 1% of hereditary colon cancer, is associated with pathogenic variants in the *APC* gene. The *APC* gene encodes a multi-functional protein that may participate in several cellular processes such as cell adhesion and migration, signal transduction, microtubule assembly, and chromosome segregation [3]. Individuals who have familial adenomatous polyposis develop hundreds to thousands of adenomatous colonic polyps, beginning, on average, at age 16 years (range 7–36 years) [4]. Without colectomy, colon cancer is typically inevitable for these patients.

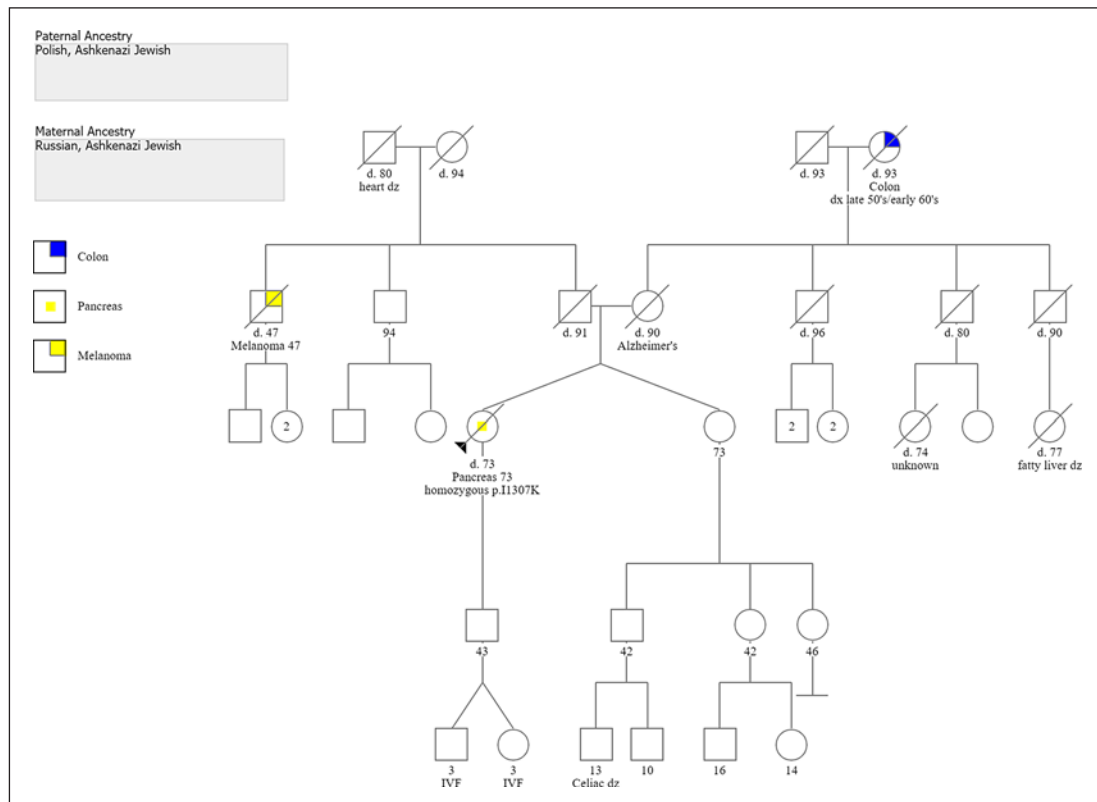
A specific variation in the *APC* gene, called p.I1307K, is a risk allele associated with a moderate risk for colon cancer, but not polyposis. While most disease-causing *APC* pathogenic variants result in the production of a truncated nonactive protein, the p.I1307K substitution does not change the *APC* protein structure but rather results in a hypermutable region [5]. The prevalence of the p.I1307K variant in the general Ashkenazi Jewish (AJ) population is approximately 10% among average risk asymptomatic AJ individuals [5]. The colorectal cancer risk is estimated to be increased 1.75-fold [5], and this risk appears to be primarily limited to Ashkenazi Jews [6]. The current National Comprehensive Cancer Network (NCCN) guidelines (Version 1.2021) recommend that p.I1307K heterozygotes without a personal history of colorectal cancer undergo colonoscopy screening every 5 years beginning at age 40 or 10 years prior to the age of a first-degree relative's colon cancer diagnosis (if applicable) [7]. In p.I1307K heterozygotes who are affected with colorectal cancer, the NCCN recommends surveillance based on the pathologic stage of the individual's colorectal cancer [8]. In contrast, for individuals who are homozygous for the p.I1307K variant, data are much more limited, and there are currently no screening recommendations.

This case series includes 4 patients identified through genetics clinics who are homozygous for the *APC* p.I1307K variant. While *APC* p.I1307K heterozygotes are common in individuals of AJ ancestry, there are few reports that discuss homozygous cases. This case series provides additional information about the clinical spectrum that may be associated with the homozygous p.I1307K genotype.

## Case Report/Case Presentation

### *Clinical Case I*

Patient 1 is a 73-year-old AJ female who was originally referred to genetics in January 2020 to discuss germline genetic testing due to a recent diagnosis of metastatic pancreatic adenocarcinoma. GI screening history includes a colonoscopy in 2010 which did not identify any colon polyps. She had an upper endoscopy in the December of 2019 in preparation for cholecystectomy. The patient did not undergo cholecystectomy due to jaundice, workup for which prompted a stent placement in her bile duct, which ultimately led to her pancreatic cancer diagnosis. Patient 1 was subsequently diagnosed with metastatic pancreatic adenocarcinoma with metastasis to the liver; staging with biomarkers is as follows: positive CK7 and MOC31, negative HepPar 1, MSI stable, TMB intermediate (9 mutations), KRAS pathogenic variant exon 2, APC, CDKN2A, KRAS, and TP53 pathogenic variants, and PD-L1 (SP142) biomarker negative.



**Fig. 1.** Family history/pedigree for patient 1.

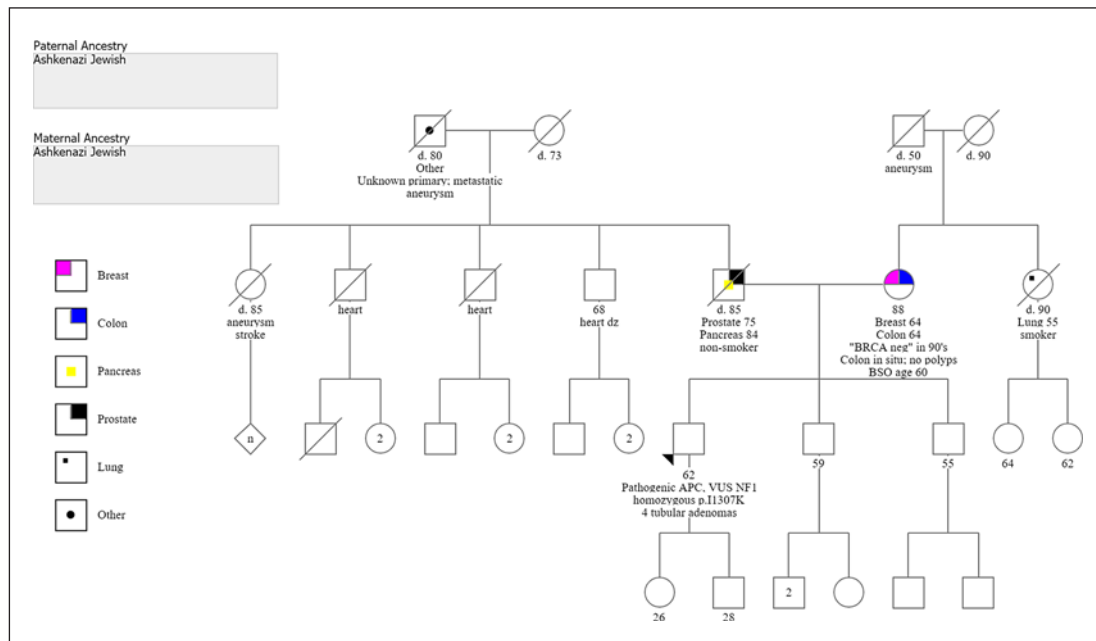
Family history is represented in Figure 1 and is negative for polyposis. Significant family history of cancer includes a paternal uncle who was diagnosed with melanoma at age 47 and a maternal grandmother who was diagnosed with colon cancer in her late 50s or early 60s.

A 36-gene panel was ordered for patient 1 with concurrent DNA and RNA analysis. This testing revealed homozygous APC p.I1307K variants. No other pathogenic or uncertain variants were identified. The patient was referred for follow-up colonoscopies and continuing pancreatic cancer treatment. However, she declined all follow-up and transitioned to palliative care, dying shortly after. Her fraternal twin sister was subsequently seen in clinic for familial genetic testing. She was found to be heterozygous for the familial variant.

### Clinical Case II

Patient 2 is a 62-year-old AJ male who was referred to genetics due to a family history of breast, colon, ovarian, pancreatic, and prostate cancers. Family history is represented in Figure 2. He first had a colonoscopy at age 54, which found 1-subcentimeter tubular adenoma. He had an upper endoscopy at 58 years old, which showed mild gastritis and multiple fundic gland polyps. The patient has a history of GERD and PPI use. He had a repeat colonoscopy at age 59, which found one 5-mm polyp (tubular adenoma) in the ascending colon. Subsequent colonoscopy at age 62 revealed 2 polyps: a 5-mm polyp (tubular adenoma) in the ascending colon and a 2-mm polyp (tubular adenoma) in the transverse colon.

The patient reported a family history of breast cancer and colon cancer in his mother at age 64, prostate cancer (at age 75) and pancreatic cancer (at age 84) in his father, and a more distant family history of ovarian cancer, lung cancer, and widely metastatic cancer of unknown origin. There is no reported family history of colon polyposis. A 34-gene panel performed on



**Fig. 2.** Family history/pedigree for patient 2.

patient 2 revealed homozygous APC p.I1307K variants and a variant of unknown significance in NF1.

### Clinical Case III

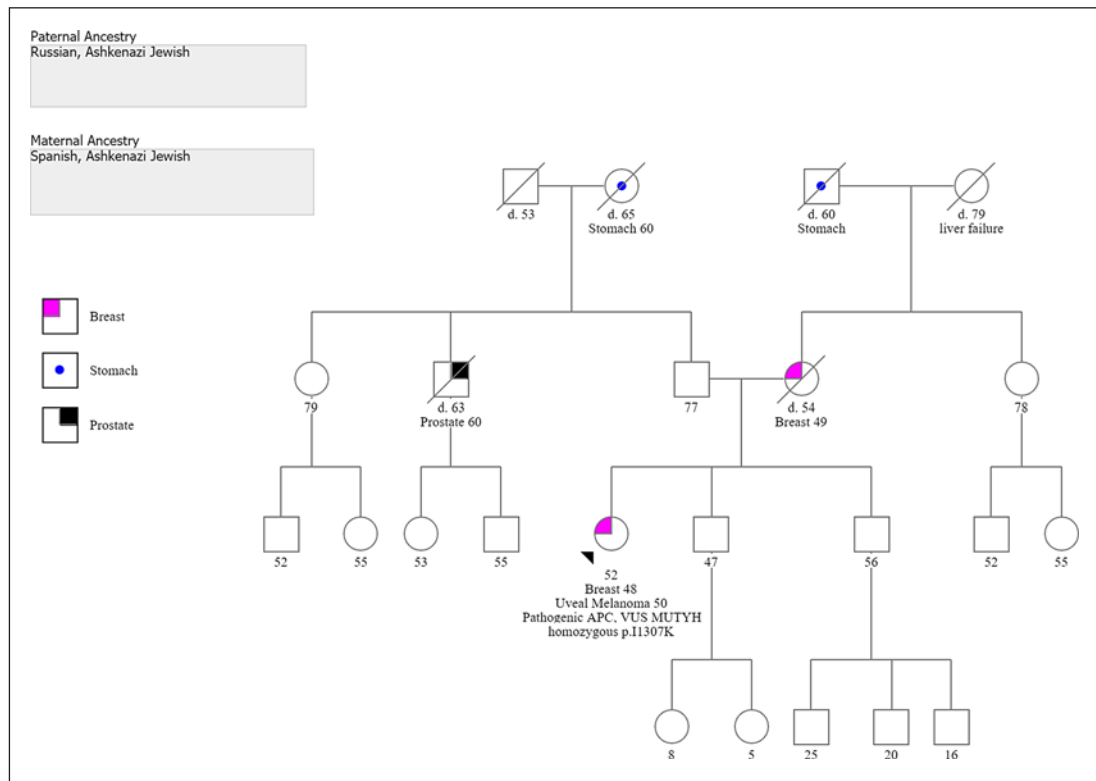
Patient 3 is a 52-year-old AJ female referred to the Hereditary Cancer Clinic to discuss genetic testing for her early-onset breast cancer. At the age of 48, the patient had been diagnosed with a left-sided stage IIA ER/PR+ breast cancer, which was treated with a bilateral mastectomy and adjuvant chemotherapy. She took tamoxifen for approximately 14 months, but discontinued use due to an adverse reaction. At the time of her initial diagnosis, the patient underwent genetic testing for *BRCA1* and *BRCA2* which was negative. In 2018, at the age of 50, the patient was diagnosed with a uveal melanoma involving the left iris. She was treated with plaque brachytherapy with excellent response and is being followed closely. Colonoscopy screening at the age of 51 was normal, with recommended follow-up in 5 years.

The patient reported a family history of breast cancer at the age of 49 in her mother, stomach cancer in her maternal grandfather and paternal grandmother, both at the age of 60, and prostate cancer in a paternal uncle at the age of 60. The family history is depicted in Figure 3.

The patient elected to pursue genetic testing for a 42-gene common hereditary cancer panel. She was found to be homozygous for the APC p.I1307K variant, as well as carry a variant of uncertain significance in the *MUTYH* gene. Although the genotype of her brothers is unknown, both were reported to have had normal colonoscopy screening. Her diagnosis of uveal melanoma was following her genetic testing that revealed the homozygous APC p.I1307K variant; no subsequent testing for *BAP1* has yet been completed.

### Clinical Case IV

Patient 4 is a 70-year-old male of AJ decent referred for genetic counseling due to a diagnosis of stage IV gallbladder adenocarcinoma and a family history of early-onset breast cancer.



**Fig. 3.** Family history/pedigree for patient 3.

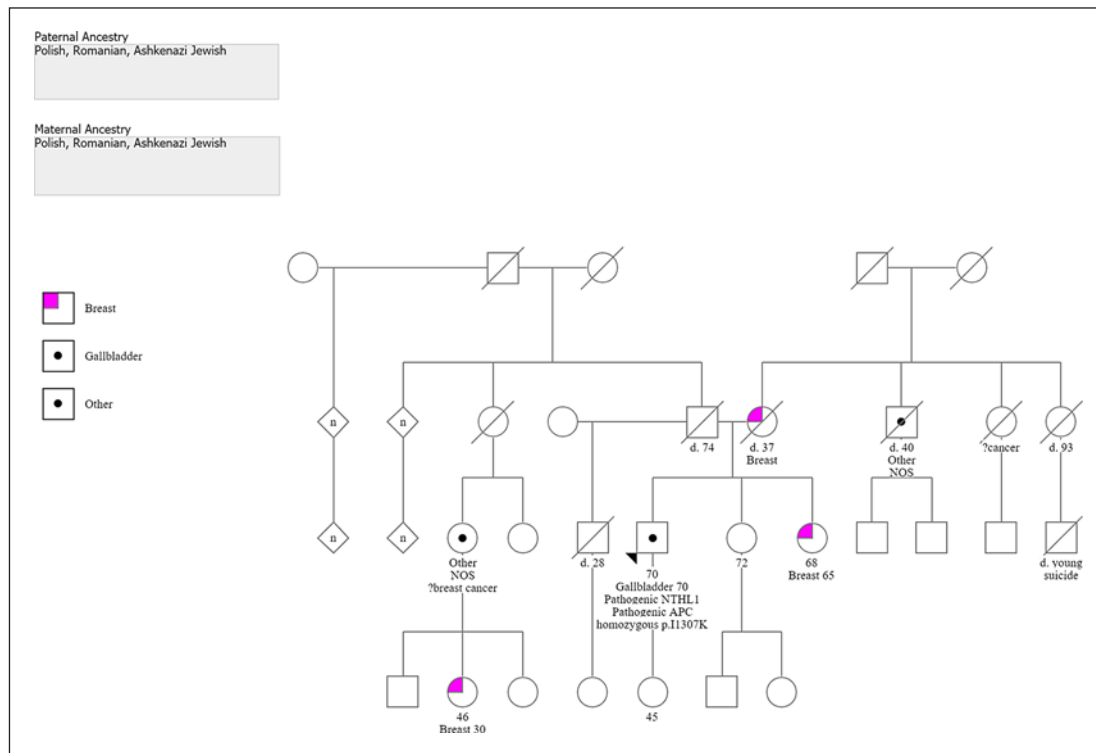
He also reported a history of several basal cell carcinomas of the face and head. His most recent colonoscopy screening from 2020 was normal, with no polyps found. He underwent FoundationOne analysis of his gallbladder tumor which revealed a somatic SMAD4 mutation identified as Y353 (c.1058A>G) and an *STK11* mutation identified as S216F (c.647C>T). Microsatellite status and tumor mutation burden could not be determined.

Family history is represented in Figure 4 and is negative for known polyposis. Significant family history of cancer includes a sister who was diagnosed with breast cancer at 65 years of age and the mother who was diagnosed with breast cancer and died at 37 years of age. A maternal uncle was diagnosed with an unspecified type of cancer and died at 40 years of age. Additionally, a paternal cousin was diagnosed with an unspecified type of cancer, possibly breast cancer, and had a daughter who was diagnosed with breast cancer in her 30s.

Germline analysis of a 47-gene panel revealed homozygous APC p.I1307K variants. A heterozygous pathogenic variant in the *NTHL1* gene identified as p.Gln90\* was also detected. The patient is currently receiving palliative gemcitabine plus cisplatin. Genetic counseling with consideration for genetic testing was recommended for close relatives.

### Discussion/Conclusion

The p.I1307K variant in the *APC* gene is a well-documented risk allele in the heterozygous state. There are few reports, however, of homozygous p.I1307K carriers. Here, we describe 4 p.I1307K homozygotes identified through genetics clinics with variable clinical presentations.



**Fig. 4.** Family history/pedigree for patient 4.

Case 1 is a 73-year-old pancreatic cancer patient with a family history of melanoma and colon cancer. Case 2 is a 62-year-old patient with a personal history of 4 adenomatous colorectal polyps and a family history of breast, pancreatic, colon, and prostate cancers. Case 3 is a 52-year-old patient with a personal history of early-onset breast cancer and uveal melanoma and a family history of breast, prostate, and stomach cancers. Case 4 is a 70-year-old patient with a personal history of gallbladder adenocarcinoma and a family history of breast cancer.

Although classic *APC* pathogenic variants are associated with colorectal polyposis, it is typically not present in individuals who are heterozygous for the p.I1307K variant nor was it documented in any of the current cases. All 4 patients presented here did have a personal and/or family history of cancer, including breast cancer and/or pancreatic cancer (Table 1). While this cancer history was the indication for gene panel testing, it may be unrelated to the p.I1307K finding. Notably, none of these probands have had a personal history of colorectal cancer. This is an interesting finding, since heterozygous p.I1307K variant carriers have a modestly increased risk for colorectal cancer, and it may be hypothesized that homozygous carriers could potentially have even higher risks. The fact that pathogenic variants in many cancer genes result in a more severe phenotype when present in a biallelic state supports this hypothesis [9–11].

This case series builds upon a relatively small number of previously reported homozygous *APC* p.I1307K variant carriers. Zauber et al. [12] described a 28-year-old AJ female who presented with a desmoid tumor; this patient had a family history of colon cancer in a grandfather and breast cancer in a grandmother. Zauber et al. [13] subsequently reported 2 additional homozygous p.I1307K patients: one with 3 tubular adenomas and the other with cecal carcinoma and 2 adenomas, 1 tubular and 1 tubulovillous, at age 71 years.

**Table 1.** Table describing phenotypes, screening findings, and family history of each patient

|                          | Patient 1   | Patient 2   | Patient 3  | Patient 4   |
|--------------------------|---|---|--|---|
| Age(s) of colonoscopy    | 63  | 54, 59, 62  | 51   | 70  |
| Colonoscopy findings     | No polyps   | 4 tubular adenomas  | No polyps  | No polyps   |
| EGD                      | None  | Fundic gland polyps on EGD  | None   | None  |
| Personal cancer history  | Pancreatic cancer diagnosed age 73  | None  | Breast cancer age 48<br>Uveal melanoma age 50  | Gallbladder adenocarcinoma diagnosed age 70   |
| Family history of cancer | No family history of colon polyps<br>Paternal uncle melanoma age 47<br>Maternal grandmother colon cancer late 50s–early 60s | Mother breast cancer age 64,<br>colon cancer age 64<br>Father prostate cancer age 75,<br>pancreatic cancer age 84 | Mother breast cancer age 49<br>Maternal grandfather stomach cancer age 60<br>Paternal uncle prostate cancer age 60<br>Paternal grandfather stomach cancer age 60 | Sister breast cancer age 65<br>Mother breast cancer age 37<br>Maternal uncle unknown cancer age 40<br>Paternal cousin unknown cancer, possibly breast<br>Paternal first cousin once removed breast cancer age 30s |

All 4 patients in the current series were tested due to personal or family history of cancer, presumably looking for pathogenic variants in genes like *BRCA1/2* which are associated with breast and pancreatic cancer and are also present at a higher frequency in AJ individuals. Therefore, in some cases, homozygous *APC* p.I1307K variants could represent incidental findings, and the personal and family histories of breast and pancreatic cancers may be the result of ascertainment bias. However, the possibility that the *APC* p.I1307K variant could be associated with an increased risk for noncolorectal cancer risk has been questioned, although not as extensively. A recent study by Leshno et al. [14] provided evidence that the variant may in fact confer other cancer risks, including breast and pancreatic. Thus, whether the *APC* variant may have contributed to the cancer history in the described cases is not currently understood.

The p.I1307K variant is present in approximately 10% of individuals of AJ ancestry and has also been reported in individuals without known Jewish ancestry, although at a lower frequency and without similar colorectal cancer risks [6]. Given the relatively high prevalence of this variant in AJ individuals, it is somewhat unexpected that so few reports of *APC* p.I1307K homozygosity are present in the literature. The current case series helps contribute to the clinical phenotype which may exist with this seemingly rare genotype. While the spectrum of features reported thus far ranges from unaffected to desmoids to breast cancer and pancreatic cancer, it is unknown if these tumors and cancers are actually part of the phenotypic spectrum or simply the result of ascertainment bias. Thus, the significant clinical variability seen in the current cases as well as in the few previously published cases makes cancer screening guidelines for p.I1307K homozygotes a particularly challenging yet important question. Additional studies are needed to help better characterize and define *APC* p.I1307K homozygosity-associated risks and implications for cancer treatment and surveillance.



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## Statement of Ethics

All subjects have given their written informed consent to publish their case, and consent is available at request. Pedigrees were constructed by genetic counselors. All patients are identified by aliases and not by their real names. This study is exempt from ethics committee approval as the data are anonymized and the study is a low-risk health study involving no risk to the subjects.

## Conflict of Interest Statement

All authors declare no conflicts of interest.

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## Author Contributions

Drafts were written by Alexa Rosenblum, Amanda Eppolito, and Michelle Springer. Edits and updates were contributed by all 5 authors. All 5 authors worked collaboratively to make sure all relevant details were added to each separate case report.

## Data Availability Statement

All data generated or analyzed during this study are included in this article and its online suppl. material, see [www.karger.com/doi/10.1159/000518683](http://www.karger.com/doi/10.1159/000518683). Further inquiries can be directed to the corresponding author.

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