








OPEN ACCESS

# Position statement of the International Society for Gastrointestinal Hereditary Tumours (InSiGHT) on APC I1307K and cancer risk

Laura Valle <sup>1,2,3</sup>, Lior H Katz,<sup>4</sup> Andrew Latchford <sup>5,6</sup>, Pilar Mur <sup>1,2,7</sup>, Victor Moreno <sup>2,8,9,10,11</sup>, Ian M Frayling <sup>12</sup>, Brandie Heald <sup>13</sup>, Gabriel Capellá <sup>1,2,3</sup> on behalf of the InSiGHT Council

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/jmg-2022-108984>).

For numbered affiliations see end of article.

## Correspondence to

Dr Gabriel Capellá, Hereditary Cancer Program, Catalan Institute of Oncology, IDIBELL, Hospitalet de Llobregat, Barcelona, Spain; [gcapella@idibell.cat](mailto:gcapella@idibell.cat)

LV and LHK are joint first authors.

Received 7 October 2022  
Accepted 1 March 2023  
Published Online First 19 April 2023

## ABSTRACT

While constitutional pathogenic variants in the APC gene cause familial adenomatous polyposis, APC c.3920T>A; p.Ile1307Lys (I1307K) has been associated with a moderate increased risk of colorectal cancer (CRC), particularly in individuals of Ashkenazi Jewish descent. However, published data include relatively small sample sizes, generating inconclusive results regarding cancer risk, particularly in non-Ashkenazi populations. This has led to different country/continental-specific guidelines regarding genetic testing, clinical management and surveillance recommendations for I1307K. A multidisciplinary international expert group endorsed by the International Society for Gastrointestinal Hereditary Tumours (InSiGHT), has generated a position statement on the APC I1307K allele and its association with cancer predisposition. Based on a systematic review and meta-analysis of the evidence published, the aim of this document is to summarise the prevalence of the APC I1307K allele and analysed the evidence of the associated cancer risk in different populations. Here we provide recommendations on the laboratory classification of the variant, define the role of predictive testing for I1307K, suggest recommendations for cancer screening in I1307K heterozygous and homozygous individuals and identify knowledge gaps to be addressed in future research studies. Briefly, I1307K, classified as pathogenic, low penetrance, is a risk factor for CRC in individuals of Ashkenazi Jewish origin and should be tested in this population, offering carriers specific clinical surveillance. There is not enough evidence to support an increased risk of cancer in other populations/subpopulations. Therefore, until/unless future evidence indicates otherwise, individuals of non-Ashkenazi Jewish descent harbouring I1307K should be enrolled in national CRC screening programmes for average-risk individuals.

## INTRODUCTION

Unlike known pathogenic variants in the APC gene, which cause familial adenomatous polyposis, APC (NM\_000038.6) c.3920T>A; p.Ile1307Lys (from herein on I1307K), has been suggested to predispose to colorectal cancer (CRC), but not polyposis. This variant results in the substitution of an isoleucine for a lysine at codon 1307, located in the  $\beta$ -catenin binding domain of APC. The affected residue is highly conserved (conservation=0.9 from 38 aligned protein sequences), but isoleucine and lysine show moderate physicochemical

## WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ APC I1307K causes moderate increased risk of colorectal cancer in individuals of Ashkenazi Jewish descent, where the variant prevalence is the highest.
- ⇒ Colorectal cancer risk in non-Ashkenazi Jews and in non-Jewish individuals, risk of extracolonic cancers and risk of cancer in homozygous individuals are not yet fully understood.

## WHAT THIS STUDY ADDS

- ⇒ This study summarises the available evidence on the prevalence of APC I1307K allele in different populations and their associated risks of different cancer types.
- ⇒ Based on the available evidence on the functional effect of the variant, the association with colorectal cancer in different populations and with different cancer types, we propose recommendations for the classification of the variant, cancer screening in heterozygous and homozygous individuals, and predictive testing.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Our recommendations may help standardise/homogenise laboratory reports and clinical recommendations for I1307K heterozygous and homozygous individuals among countries.
- ⇒ Our study informs on the strengths and limitations of the evidence available for APC I1307K leading to the identification of knowledge gaps to be addressed in future research.

differences (Grantham distance: 102 (0–215)). While in silico tools predict a benign effect of the variant on protein function (VarSome: 9/12 benign predictions),<sup>1</sup> I1307K has been shown to modestly alter  $\beta$ -catenin-regulated transcription in vitro.<sup>2</sup> Interestingly, the c.3920T>A nucleotide change affects an (A)3(T)(A)4 sequence element, converting it into an extended tract of eight adenosine nucleotides (A8). *In vivo* and *in vitro* studies have shown that this substitution results in the slippage of the polymerase during DNA replication, conferring an increased propensity for somatic truncating mutations on this allele.<sup>3,4</sup>



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

**To cite:** Valle L, Katz LH, Latchford A, et al. *J Med Genet* 2023;**60**:1035–1043.

Despite the experimental evidence, the lack of association of the variant with a Mendelian syndrome prevents its classification following the consensus recommendations of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP).<sup>5</sup> In fact, this variant has conflicting interpretations of pathogenicity across laboratories and in ClinVar ([https://www.ncbi.nlm.nih.gov/clinvar/variation/822/?oq=APC\[gene\]+AND+p.Ile1307Lys\[-varname\]+&m=NM\\_000038.6\(APC\):c.3920T%3EA%20\(p.Ile1307Lys\)](https://www.ncbi.nlm.nih.gov/clinvar/variation/822/?oq=APC[gene]+AND+p.Ile1307Lys[-varname]+&m=NM_000038.6(APC):c.3920T%3EA%20(p.Ile1307Lys))).

APC I1307K is present in population databases (rs1801155; minor allele frequency=0.18%; source: Genome Aggregation Database (gnomAD) v.2.1.1), with the highest frequency in individuals of Ashkenazi Jewish (AJ) ancestry (MAF<sub>gnomAD</sub>=3.6%; ~1/28). Several studies have associated this variant with a moderate increase in the risk of CRC in individuals of AJ ancestry, where this variant is found in ~6%–10% of the population<sup>3,6</sup> and in ~15%–28% of individuals with family history of CRC.<sup>3,7</sup> However, I1307K is also present in ~2.5% of Sephardi Jewish (SJ) individuals<sup>6</sup> and much less frequently in non-Jewish populations (<0.15% in European, Asian, Latino or African populations).<sup>2,8–10</sup> Anthropological data suggest that this variant likely arose between 947 BC and 195 BC, preceding, or coinciding with, the Jewish diasporas.<sup>11,12</sup> Its high representation in the Ashkenazi population can be explained by a genetic drift caused by a specific founder effect in the Ashkenazim, plus a lack of negative selection.<sup>11</sup>

Based on the reported association of APC I1307K with moderate increased risk of CRC, current National Comprehensive Cancer Network (NCCN) guidelines recommend CRC surveillance for individuals with the I1307K variant, regardless of their ethnicity (Genetic/Familial High-Risk Assessment: Colorectal Cancer; V.2.2022; [https://www.nccn.org/professionals/physician\\_gls/pdf/genetics\\_colon.pdf](https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf)). Nevertheless, whether the associated cancer risk affects any carrier regardless of his or her ethnicity or is restricted to AJ, remains a topic of debate and needs to be clarified to refine the clinical recommendations.

The aim of this document is to summarise the available evidence on the prevalence of APC I1307K allele in different populations and their associated risks of cancer. This evidence will be used to make recommendations on the laboratory classification of the variant, the role of predictive testing for I1307K and recommendations for cancer screening for I1307K heterozygous and homozygous individuals.

## METHODS

### Systematic review of the literature

A bibliography search using Ovid, MEDLINE, Embase, Cochrane CENTRAL, Scopus and Web of Science was performed using search terms “I1307K” AND “APC” AND “variant”. A manual PubMed (<https://www.ncbi.nlm.nih.gov/pubmed/>) search was performed using the terms “I1307K” AND “APC” AND “variant”. In total, 1256 articles were identified. These articles were independently reviewed by AL, BH and PM for inclusion/exclusion. Publications that were not in English were excluded. Publications were included if they provided data related to the questions to be addressed by this study: prevalence of I1307K in AJ and non-AJ cohorts, cancer risks associated with I1307K, constitutional I1307K homozygosity, I1307K functional analyses, I1307K founder effects and management recommendations for I1307K carriers. If AL and BH agreed, the article was selected for inclusion. If AL and BH disagreed, the articles were reviewed by all authors for inclusion/exclusion. In total, 65 articles were

included after duplications, and irrelevant articles were excluded (online supplemental table 1). This review was not registered.

### Population data

In addition to the data reported in the publications, the frequency of the APC I1307K allele in populations was obtained from the Genome Aggregation Database (gnomAD V.2.1.1 and V.3.1.2, non-cancer datasets),<sup>8</sup> the Collaborative Spanish Variant Server (<http://csvs.babelomics.org/>)<sup>13</sup> and the SweGen Project (<https://swefreq.nbis.se/dataset/SweGen/browser/>)<sup>14</sup> (access date: December 2022). The frequency of APC I1307K in Spanish CRC cases and controls was obtained from the case–control study MCC-Spain (<https://shiny.snpstats.net/exome/>)<sup>15</sup> (access date: December 2022).

### Statistical analyses

Fisher’s exact test (two sided) and logistic regression were used to compare frequencies between cases and controls. Results were considered statistically significant when  $p < 0.05$ . Statistical tests, odds ratios (ORs) and CIs calculations were carried out using RStudio Cloud.

## QUESTIONS ADDRESSED

### How are Ashkenazi and Sephardi Jewish heritages defined?

Considering the importance of assessing an Ashkenazi ancestry, we herein review the definition of the AJ population and how it has been assessed in the published reports to make appropriate recommendations in the clinical setting.

AJs are defined as Jews of Eastern European origin. They constitute more than 80% of the worldwide Jewry.<sup>16</sup> Originally, this Jewish diaspora population coalesced in Germany around the end of the first millennium. In the late Middle Age, due to religious persecution, most of the Ashkenazi population shifted steadily eastward, moving into the areas comprising parts of present-day Belarus, Estonia, Latvia, Lithuania, Moldova, Poland, Russia, Slovakia and Ukraine. Later, AJs emigrated to the USA and other parts of Eastern and Western Europe. After the Holocaust, many of the surviving AJs emigrated outside Europe to countries such as Israel, Canada, Argentina, Australia or the USA.<sup>17,18</sup>

AJs can be defined by religion, culture or ethnicity; however, it is their genetics that can unequivocally group them, regardless of the geographic location, since they are a homogenous genetic cohort. Several genetic or genomic approaches, focused on genome-wide genetic signatures<sup>19–21</sup> or on Y chromosome and mitochondrial DNA lineages<sup>22–25</sup> may be undertaken to determine AJ heritage. Surprisingly, none of the published studies on APC I1307K have defined AJs following genetic criteria. In fact, the inclusion criteria of the published reports are heterogeneous, with a significant number of them providing no information. Most studies base the definition of AJs on self-identification or information about the country of birth of the patients and their parents. The country of birth of the grandparents was included in some of the studies. Mixed origin can be often found in the clinical setting, but this has also been considered differently among publications. While some studies required both parents or all four grandparents of the subject to be considered Ashkenazim,<sup>26,27</sup> others required only one parent to be an AJ.<sup>7,28,29</sup> Other studies did not specify which criteria for the definition of AJ were used.<sup>3,30–35</sup> In all cases, information was based on either self-reporting or data included in the individuals’ medical records (online supplemental table 1).

**Table 1** Published studies and meta-analysis of constitutional APC I1307K in AJ CRC patients and AJ controls

Study	AJ individuals		OR (95% CI), p value*
	CRC cases I1307K/total (%)	Controls I1307K/total (%)	
Laken <i>et al</i> (1997) <sup>3</sup>	22/211 (10.43)	47/766 (6.14)	1.78 (0.99 to 3.10), p=0.047
Woodage <i>et al</i> (1998) <sup>30</sup>	7/55 (12.7)	355/4948 (7.2)	1.88 (0.71 to 4.23), p=0.12
Rozen <i>et al</i> (1999) <sup>7</sup>	3/51 (5.9)†	6/120 (5.0)	1.19 (3.18 to 5.83), p=1
Drucker <i>et al</i> (2000) <sup>27</sup>	12/71 (16.9)	17/298 (5.7)	2.15 (0.88 to 5.12), p=0.07
Shtoyerman-Chen <i>et al</i> (2001) <sup>31</sup>	29/227 (12.77)	8/148 (5.41)	2.56 (1.1 to 6.77), p=0.02
Stern <i>et al</i> (2001) <sup>28</sup>	6/22 (27.27)	17/209 (8.13)	4.19 (1.19 to 13.30), p=0.01
Figer <i>et al</i> (2001) <sup>59</sup>	8/50 (16.0)	8/148 (5.4)	3.31 (1.02 to 10.80), p=0.03
Rozen <i>et al</i> (2002) <sup>26</sup>	6/77 (7.8)	12/194 (6.2)	1.28 (0.38 to 3.86), p=0.6
Strul <i>et al</i> (2003) <sup>38</sup>	26/267 (9.7)	17/204 (8.33)	1.19 (0.60 to 2.40), p=0.6
Fidder <i>et al</i> (2005) <sup>60</sup>	35/322 (10.9)	13/260 (5)	2.31 (1.16 to 4.88), p=0.015
Boursi <i>et al</i> (2013) <sup>6</sup>	37/299 (12.3)	86/1089 (7.9)	1.65 (1.06 to 2.51), p=0.02
Forkosh <i>et al</i> (2022) <sup>10</sup>	145/1306 (11.1)	342/4918 (6.9)‡	1.67 (1.35 to 2.06), p=1.8 x 10 <sup>-6</sup>
Gryfe <i>et al</i> (1999) <sup>37</sup>	41/404 (10.1)	–	–
Figer <i>et al</i> (2001) <sup>32</sup>	23/189 (12.17)	–	–
Zauber <i>et al</i> (2003) <sup>61</sup>	22/182 (12.1)§	–	–
Rennert <i>et al</i> (2005) <sup>42</sup>	71/633 (9.6)	–	–
Zauber <i>et al</i> (2005) <sup>34</sup>	12/74 (16.2)	–	–
Locker <i>et al</i> (2006) <sup>29</sup>	26/215 (12.1)	–	–
Ukaegbu <i>et al</i> (2021) <sup>35</sup>	35/285 (13)	–	–
Total	566/4940 (11.5)	928/12945 (7.2)	1.68 (1.50 to 1.87), p<2.2 x 10 <sup>-16</sup> 1.78 (1.54 to 2.06), p<0.00001¶

\*Fisher's exact test. Calculations made for this publication. Results may not coincide with the original publications due to the application of different adjustments to the tests in their analyses.

†Individuals with personal or family history of colorectal neoplasia (CRC or adenoma).

‡Control data obtained from gnomAD.

§172 patients with colorectal neoplasia (CRC or adenoma) and 10 first-degree relatives without neoplasia.

¶Logistic regression.

AJ, Ashkenazi Jewish; CRC, colorectal cancer.

SJ are a Jewish diaspora population who coalesced in the Iberian Peninsula (Spain and Portugal). Most of this population was expelled from that area during the late 15th century to North Africa, Western Asia, Southern Europe and some parts of America. During the 20th century, many of them emigrated to Israel. The current use of the term SJ is mostly religious and does not consider ethnicity.<sup>36</sup> Whether the use of genomic markers is useful to identify SJ heritage is not known.

We recommend that a thorough assessment of AJ ancestry is performed by asking about the individual's Jewish ancestry, and the country of birth of, at least, the individual and his or her parents. Ideally, the country of birth of the grandparents should be asked for. Caution should be taken when considering AJ ancestry when only one grandparent (maternal and/or paternal) is an AJ. It must be assumed that some individuals may not be aware of their AJ heritage.

For future research studies, we recommend evaluating the putative utility of genetic criteria to define AJ ancestry in the settings of genetic counselling and clinical research. The use of genetic signatures might help identify heritages more accurately.

#### What is the risk of CRC in AJs with the APC I1307K variant?

For over two decades, numerous studies have explored the association between APC I1307K and the risk of CRC in different ethnic populations, including specific studies in AJs. We performed a meta-analysis combining 19 studies that included AJ CRC patients. This analysis showed that I1307K is present in 11.5% (566/4940) of AJ CRC patients and in 7.2% (928/12 945) of AJ CRC-free controls, which translates into an OR of 1.68 (95% CI 1.50 to 1.87; p<0.00001; Fisher's exact test) (table 1).

A logistic regression test adjusted by study showed similar results (OR=1.78; 95% CI 1.54 to 2.06; p<0.00001), either including or excluding the studies without controls.

Most studies published to date show that the mean age at CRC diagnosis in I1307K heterozygotes ranges between ~60 and 70 years, being similar to the age at diagnosis in wildtype patients (between 0 and 2 years younger in carriers) (online supplemental table 1).<sup>29 32–34 37 38</sup>

The APC I1307K variant has been occasionally found in patients with multiple adenomas or adenomatous polypsis,<sup>2 3 28 33 34 37 39–42</sup> however, in most cases, this was likely caused by ascertainment bias. Most comparative studies indicate that I1307K heterozygotes are not more susceptible to develop multiple adenomas than wildtype individuals.<sup>28 33</sup> Likewise, available data suggest that there are no differences in the age at the time of the first adenoma diagnosis.<sup>34</sup> Rennert *et al*<sup>42</sup> observed that I1307K heterozygotes were significantly more likely to have colorectal polyps than wildtype individuals after age-adjustment (51.3% vs 33.6%; p=0.03), however, the number of polyps did not differ between the two groups.

In conclusion, available evidence indicates that APC I1307K is a risk factor for CRC in AJ individuals and thus should be evaluated in this subpopulation.

#### What is the risk of CRC in non-AJ Jews with the APC I1307K variant?

As in Ashkenazim, we gathered the data published on I1307K in Jewish CRC patients and controls of non-Ashkenazi ancestry,

**Table 2** Published studies and meta-analysis of constitutional APC I1307K in non-AJ Jewish CRC patients and controls

Study	Non-AJ Jewish individuals		OR (95% CI), p value*
	CRC cases I1307K/total (%)	Controls I1307K/total (%)	
Rozen <i>et al</i> (1999) <sup>7</sup>	0/17 (0.0)†	1/188 (0.5)	0.00 (0.00 to 428.41), p=1
Drucker <i>et al</i> (2000) <sup>27</sup>	3/38 (7.9)‡	9/189 (4.8)‡	1.62 (0.27 to 6.90), p=0.4
Shtoyerman-Chen <i>et al</i> (2001) <sup>31</sup>	2/122 (1.6)	4/370 (1.1)	1.52 (0.14 to 10.78), p=0.6
Rozen <i>et al</i> (2002) <sup>26</sup>	0/20 (0.0)§	3/199 (1.51)	0.00 (0.00 to 24.80), p=1
Fidder <i>et al</i> (2005) <sup>33</sup>	4/165 (2.42)	3/151 (1.99)	1.22 (0.20 to 8.50), p=1
Figer <i>et al</i> (2001) <sup>32</sup>	2/80 (2.5)¶	–	–
Figer <i>et al</i> (2001) <sup>39</sup>	0/25 (0.0)¶	–	–
Rennert <i>et al</i> (2005) <sup>42</sup>	5/184 (2.7)	–	–
Total	16/651 (2.5)	20/1097 (1.8)	1.36 (0.65 to 2.78), p=0.39 1.35 (0.57 to 3.19), p=0.49**

\*Fisher's exact test. Calculations made for this publication. Results may not coincide with the original publications due to the application of different adjustments to the tests in their analyses.

†Individuals with personal or family history of colorectal neoplasia (CRC or adenoma).

‡All I1307K heterozygotes are Yemenite Jews.

§Individuals with colorectal neoplasia (CRC or adenoma).

¶Some Israeli Arabs included.

\*\*Logistic regression.

AJ, Ashkenazi Jewish; CRC, colorectal cancer.

and a meta-analysis was performed. In this case, the prevalence of the variant was 2.5% (16/651) in non-AJ Jewish CRC patients and 1.8% (20/1097) in controls, showing no significant association with CRC risk ( $p=0.39$ ; Fisher's exact test) (table 2). Concordant results were obtained with a logistic regression test (OR=1.35; 95% CI 0.57 to 3.19;  $p=0.49$ ).

Available data, although scarce, indicate that APC I1307K is present in SJ.<sup>6</sup> However, few studies have addressed the associated cancer risks in this group. Drucker *et al*<sup>27</sup> did not find the variant in any of the 34 SJ CRC patients that were analysed. Boursi *et al*<sup>6</sup> identified 19 heterozygous individuals among 290 SJ CRC patients and 408 SJ controls, showing no association between carrier status and CRC (adjusted OR=1.95% CI 0.51 to 1.93).

Available data indicate that APC I1307K is not a risk factor for CRC in non-Ashkenazi Jews. Although the results are consistent among studies, data are still scarce, and additional information is needed to confirm these findings unequivocally.

### What is the risk of CRC in non-Jewish populations?

Published data on the association of APC I1307K and CRC in non-Jewish populations are relatively poor and present methodological flaws, particularly due to the lack of geographically matched controls. Moreover, most studies lack ancestry/ethnicity information, as non-Jewish cases were defined by an assumption based on the country of the study and its population demographics (eg, country-specific studies or gnomAD populations). Due to the variability of origin of the studied populations and of APC I1307K frequencies, no meta-analysis was herein performed.

The reported/available data on European or non-AJ white CRC patients are indicated in table 3, together with the data obtained from population-based European datasets. The only population-based case-control study included, MCC-Spain, shows no differences between cases and controls: 7/4072 (0.17%) CRC patients versus 4/2739 (0.15%) controls (OR=1.18; 95% CI 0.34 to 4.03;  $p=0.8$ ; logistic regression).

Interestingly, the prevalence of APC I1307K in Israeli Arabs and Egyptians might be higher than in other non-Jewish

geographical contexts (table 3). Specific studies to evaluate the cancer risk associated with I1307K in these and other populations are encouraged.

We conclude that there is no conclusive evidence to support that the I1307K allele confers increased risk of CRC in non-Jewish individuals. We encourage the publication of available data (preferably well-designed, geographically matched case-control studies) in different populations to be able to make a clinically informative statement.

### Is I1307K associated with an increased risk of other cancer types?

The influence of APC I1307K on the risk of extracolonic cancers remains unclear. APC I1307K has been reported in AJ or Israeli individuals (ethnicity not reported assuming AJ as the most common ancestry) affected with extracolonic cancer phenotypes, mainly breast, prostate and pancreatic cancers (online supplemental table 1).<sup>10 28 30 37 43–50</sup>

Based on the available data, a meta-analysis was performed to assess the risk of extracolonic cancer in APC I1307K heterozygotes of AJ descent. The data gathered indicates that the prevalence of APC I1307K is of 7.6% (588/7709) in AJ or Israeli patients affected with extracolonic cancer and of 5.8% (1239/21423) in AJ or Israeli controls, resulting in a statistically significant difference (OR=1.35; 95% CI 1.21 to 1.49) (table 4). These results should be interpreted with caution as 76% of the controls but only 18% of patients belong to the two cohorts of Israeli individuals with no reported ancestries.<sup>45 49</sup> The potential inclusion of non-AJ individuals in these two studies, which would mostly affect the control group, might have resulted in an underestimation of the prevalence of the variant in the control group. After the exclusion of these publications, the APC I1307K prevalence was 7% in extracolonic cancer patients (443/6329) and 7% in controls (359/5127) of AJ origin, suggesting no increased risk (table 4).

As mentioned previously, several studies addressed the role of APC I1307K in non-CRC cancer types (online supplemental table 1). The combined analysis of the reported

**Table 3** Published studies on APC I1307K and publicly available data in non-Jewish CRC patients and controls

Study	Non-Jewish individuals		Declared origin
	CRC cases I1307K/total (%)	Controls I1307K/total (%)	
European/non-AJ white			
Lothe <i>et al</i> (1998) <sup>62</sup>	1/210 (0.48)	–	Norwegian (I1307K heterozygote is of Jewish origin, probably AJ)
Evertsson <i>et al</i> (2001) <sup>63</sup>	0/194 (0)	–	Swedish
Kapitanovic <i>et al</i> (2004) <sup>64</sup>	0/73 (0)	–	Croatian
Zhou <i>et al</i> (2004) <sup>65</sup>	1/91 (1.1)	–	Swedish
Forkosh <i>et al</i> (2022)* <sup>10</sup>	64/26 563 (0.24)	–	Non-AJ whites (USA commercial laboratory)
Prior <i>et al</i> (1999) <sup>9</sup>	0/240 (0)	–	Italian, Finnish, Hawaiian-Japanese
MCC-Spain†	7/4072 (0.17)	4/2739 (0.15)	Spanish
CSVS non-cancer‡	–	9/2024 (0.44)	Spanish
SweGen§	–	0/1000 (0)	Swedish
gnomAD non-cancer, NFE¶	–	111/91 301 (0.12)	gnomAD V.2.1.1 (73/58 918) and V.3.1.2 (38/32 383)
Other geographic origins			
Chen-Shtoyerman <i>et al</i> (2003) <sup>66</sup>	8/24 (33.3)	–	Israeli Arabs
Rennert <i>et al</i> (2005) <sup>42</sup>	2/79 (2.5)	–	65 Israeli Arabs and 14 non-Jewish non-Arabs (I1307K heterozygotes are Arabs)
Bougatef <i>et al</i> (2009) <sup>67</sup>	1/48 (2.08)	0/63 (0)	Tunisian (no ancestry/ethnicity description)
Abdel-Malak <i>et al</i> (2016) <sup>51</sup>	22/120 (18.3)	8/100 (8)	Egyptian (no ancestry/ethnicity description)
Akcay <i>et al</i> (2021) <sup>68</sup>	0/185 (0.0)	3/490 (0.6)	Turkish (no ancestry/ethnicity description)
Dundar <i>et al</i> (2007) <sup>69</sup>	30/56 (54)	–	Turkish (no ancestry/ethnicity description)
Guo <i>et al</i> (2004) <sup>70</sup>	0/178 (0)	–	147 Chinese, 20 Malay and 11 Indian

\*Controls used by Forkosh *et al* were non-AJ whites obtained from the gnomAD dataset (gnomAD V.2.1.1 non-cancer NFE) and thus not geographically matched with the cases (USA commercial laboratory). These would largely overlap with the gnomAD non-Finnish European controls included in the table and, therefore, have not been included as matched controls for this study.

†Exome array data from MCC-Spain which includes 1348 CRC patients and 2744 controls (<https://shiny.snpstats.net/exome/>) (access date: December 2022).

‡Collaborative Spanish Variant Server: <http://csvs.babelomics.org/> (access date: December 2022).

§SweGen project includes variant information from 1000 genomes of Swedish individuals. <https://swefreq.nbis.se/dataset/SweGen/browser> (access date: December 2022).

¶gnomAD V.2.1.1 non-cancer, non-Finnish Europeans: 73/58 918; gnomAD V.3.1.2 non-cancer, non-Finnish Europeans: 38/32 383.

AJ, Ashkenazi Jewish; CRC, colorectal cancer; CSVS, Collaborative Spanish Variant Server.

studies for breast, prostate and pancreatic cancers in AJs showed that APC I1307K does not confer increased risk of breast or prostate cancer (online supplemental tables 2 and 3). Higher prevalence of the variant was observed in AJ pancreatic cancer patients (47/508; 9.2%) compared with controls (342/4918; 7%) ( $p=0.06$ ) (online supplemental table 4). A single study found associations with renal cancer and melanoma in AJs, and with melanoma, breast and prostate cancers in non-AJ white males.<sup>10</sup> Nevertheless, the small samples sizes preclude drawing conclusions.

Available data indicate that I1307K is not associated with an increased overall risk of extracolonic cancer in AJ individuals. While some associations have been suggested for specific tumour types, data are limited, and further case-control studies in larger

cohorts, and evaluating different cancer types in different ethnic populations, are required.

#### What is the cancer risk in APC I1307K homozygotes?

There is limited published data exploring the cancer risks associated with homozygosity for APC I1307K. Population-based data (source: gnomAD V.2.1.1) indicate that 0.14% (7/5179) of AJs are homozygotes for I1307K. This proportion is consistent with Hardy Weinberg equilibrium, implying neutral selection. To our knowledge, a total of 13 I1307K homozygotes have been reported in the literature.<sup>30 34 51–53</sup>

Two I1307K homozygotes were identified among 5081 (0.04%) AJ individuals. Neither subject, aged 32 and 76 years,

**Table 4** Published studies on APC I1307K in AJ or Israeli (ethnicity not reported) extracolonic cancer patients and cancer-free controls

Study	Ashkenazi Jewish individuals or Israelis (ethnicity not determined)		
	Extracolonic ca. I1307K/total (%)	Controls I1307K/total (%)	OR (95% CI), p value*
Stern <i>et al</i> (2001)(AJ) <sup>28</sup>	2/11 (18.2)	17/209 (8.1)	2.49 (0.24 to 13.54), $p=0.2433$
Forkosh <i>et al</i> (2022) (AJ) <sup>10</sup>	441/6318 (7.0)	342/4918 (7.0)	1.00 (0.87 to 1.17), $p=0.9702$
Lieberman <i>et al</i> (2007) (Israeli) <sup>49</sup>	32/404 (7.9)	266/3283 (8.1)	0.98 (0.64 to 1.44), $p=1.00$
Leshno <i>et al</i> (2016) (Israeli) <sup>45</sup>	113/976 (11.6)	614/13 013 (4.7)	2.64 (2.12 to 3.28), $p<2.2e-16$
<b>Total</b>	<b>588/7709 (7.6)</b>	<b>1239/21 423 (5.8)</b>	<b>1.35 (1.21 to 1.49), <math>p=1.883e-08</math></b>
<b>Total (only AJs)</b>	<b>443/6329 (7.0)</b>	<b>359/5127 (7.0)</b>	<b>1.00 (0.86 to 1.16), <math>p=1</math></b>

\*Fisher's exact test. Calculations made for this publication. Results may not coincide with the original publications due to the application of different adjustments to the tests in their analyses.

AJ, Ashkenazi Jewish.

had a personal history of cancer.<sup>30</sup> Also, 2 of 429 (0.47%) AJs undergoing colonoscopy at two centres in New Jersey were identified as homozygous, but they were reported together with I1307K heterozygotes, and no specific phenotypic information was included in the publication.<sup>34</sup> A study of 120 CRC patients and 100 controls from Egypt identified four homozygotes: three among the patients and one among the cancer-free controls.<sup>51</sup> A 28-year-old AJ woman with a homozygous I1307K variant and a mesenteric desmoid tumour was individually reported.<sup>52</sup> Recently, four homozygous I1307K individuals of AJ ancestry were identified. These cases exhibited a wide phenotypic spectrum including: pancreatic cancer at age 73 years; gallbladder adenocarcinoma and no colonic findings at 70 years and several basal cell carcinomas; breast cancer at 48 years, uveal melanoma at 50 years and no colonic findings at 51 years; and two adenomas and multiple fundic gland polyps between 54 and 59 years of age.<sup>53</sup>

At this time, there are insufficient data to determine if CRC or extracolonic cancer risk is further increased in I1307K homozygotes.

### Sources of heterogeneity among studies reporting on cancer risk in APC I1307K carriers

The systematic evaluation of published evidence has led to the identification of several methodological issues that merit discussion: i) Sample sizes: large studies published to date show, in general, consistent results when evaluating risks in different ethnicities/populations and for different cancer types, while discrepancies arise from small studies (tables 1–4); ii) the heterogeneity of inclusion criteria (online supplemental table 1): while most studies consider as patients those affected with the corresponding cancer type, regardless of the age at cancer diagnosis, family history of cancer or personal or family history of adenomas, some authors also include as patients individuals with adenoma(s) or unaffected subjects with family history of cancer and/or adenomas. Also, some studies exclude patients with known hereditary cancer syndromes, while others do not; iii) the nature of the patients' cohorts: while some are hospital-based prospective or retrospective series of patients with cancer, others come from hereditary cancer clinics or commercial laboratories that offer genetic testing, being these enriched in cases suspected of hereditary cancer syndromes; iv) how ancestry is defined; and v) the country of origin of the study participants, which seems particularly relevant when studying non-Jewish populations due to the different I1307K variant frequencies observed in different countries (table 3).

Analysis of the available data consistently shows an increased CRC risk associated with the presence of I1307K in AJ (OR=1.7–1.8). However, due to the heterogeneity and/or small sample sizes, the evidence for non-AJ populations is deemed as weak. Whether there are differences in the CRC risk associated with the presence of I1307K in non-AJ populations/ethnicities remains to be elucidated, and if so, also the causes of these differences which, if existent, might be related to different genomic contexts.

### How to deal with CRC risk in I1307K AJ variant carriers and their first-degree relatives (FDRs)?

APC I1307K confers a statistically significant increased risk of CRC to carriers of Ashkenazim descent with an OR of ~1.7–1.8. Available data indicate that there are no differences in the natural history of CRC (clinical and histopathological characteristics) between the cancers developed by I1307K carriers and

non-carriers<sup>6</sup> and that the ages at CRC onset are well over the age at which colonoscopy screening initiates in the general population (mean age of CRC diagnosis in AJ I1307K heterozygotes: 60–70; online supplemental table 1). Of note, no prospective randomised case–control studies evaluating the effectiveness of earlier or more frequent colonoscopies in I1307K carriers have been performed.

With an OR of ~1.7–1.8, the CRC risk of I1307K AJ heterozygotes may be considered like the risk of wildtype individuals with one CRC-affected FDR. A meta-analysis that included 42 case–control and 20 cohort studies estimated a relative risk for CRC in individuals with one FDR affected with CRC of 1.92 (95% CI 1.53 to 2.41) when considering case–control data, and 1.37 (95% CI 0.76 to 2.46) for cohort studies, and a cumulative absolute risk for CRC at 85 years of 4.8% (~1/21). The risk values were approximately doubled when the FDR had CRC before age 50.<sup>54</sup> Of note, surveillance recommendations for individuals with a CRC-affected FDR vary among the different country/continent-specific CRC or hereditary CRC management guidelines.

Based on the premise that the CRC risk associated with I1307K is similar to the risk of individuals with an FDR affected with CRC,<sup>6</sup> currently considered to have a moderate risk for CRC, the guidelines of the NCCN (V.2.2022) recommend initiating colonoscopy at age 40 years, with follow-up every 5 years, for any individual with APC I1307K that has not developed CRC, irrespective of his or her ethnicity. For individuals with I1307K and an FDR affected with CRC, colonoscopy screening is advised to begin 10 years before the relative's age at CRC diagnosis, if that age is prior to 40 years. For individuals with I1307K and CRC, standard surveillance recommendations for post-colon or rectal cancer resection is recommended, regardless of the patient's ethnicity. Worldwide, hereditary CRC guidelines do not include management recommendations for individuals with I1307K without family history of CRC.

Recently, Breen *et al*<sup>55</sup> showed, considering an OR of 1.96 for the I1307K variant based on CRC risk estimates by Ma *et al* (2014, meta-analysis considering data in AJ and Israeli Jews)<sup>56</sup> and SEER cancer statistics (2014–2018) for population CRC risk (<https://seer.cancer.gov/statistics/>), that APC I1307K AJ heterozygotes reach a CRC risk of ~0.40% at age 40–44 years, which is the risk level of a 45–49 year-old individual at average (population) risk, and a CRC risk of ~0.7% at age 45–49 years, the risk level of a 50–54 year-old individual at average (population) risk.<sup>55</sup> However, the meta-analysis that we have performed almost one decade after the analysis by Ma *et al*, which includes more individual studies, indicates that the OR for CRC risk in AJs is 1.7–1.8 (table 1), that is, slightly lower than the 1.96 used by Breen *et al*. Moreover, as mentioned before, reported studies consistently show no earlier age of CRC onset in I1307K AJ heterozygotes compared with wildtype AJs,<sup>29 32–34 37 38</sup> not supporting an earlier start in colonoscopy screening.

Given the available data, screening by colonoscopy at the age of 45–50 years, repeating it every 5 years (and not every 10 years as recommended for average risk population), may be considered in AJ I1307K heterozygotes, with or without family history. Based on the scarce data on I1307K homozygotes, which do not support more aggressive cancer phenotypes and/or earlier ages at cancer onset, the same recommendations as for heterozygotes should be considered.

We recommend predictive testing for FDRs. Predictive testing may be considered for second-degree relatives when the FDR does not undergo testing. When genetic testing is not available,

surveillance recommendations for individuals with an FDR with CRC may be advised in FDR of I1307K carriers.

### How to deal with CRC risk in I1307K heterozygotes in non-AJs and non-Jewish population?

Available data suggest that *APC* I1307K is not a risk factor for CRC in non-AJs. However, there is insufficient evidence to determine whether the I1307K allele confers increased risk of CRC in non-Jewish individuals.

In these settings (non-AJ Jews and non-Jewish individuals), we consider sufficient to recommend carriers to be enrolled in their respective national screening programmes, taking into consideration that the start age is set at 45 or 50 years in most countries. If earlier and/or enhanced surveillance is considered, patients should be informed that they may not be at increased risk and therefore that earlier colonoscopy may not provide any benefit. Accordingly, we do not recommend predictive testing for FDRs. In the presence of family history of CRC, current recommendations for individuals with an FDR with CRC may be advised.

### How should the *APC* I1307K be classified in a laboratory report?

Based on an OR of 1.7–1.8 for CRC in AJs with the *APC* I1307K variant and a plausible mechanism of action, we recommend classifying this variant as ‘pathogenic, low penetrance’, following the ClinGen Low Penetrance/Risk Allele Working Group for Mendelian conditions (<https://clinicalgenome.org/working-groups/low-penetrance-risk-allele-working-group/>), despite not dealing with a Mendelian syndrome.

Also, we recommend adding the following information to the laboratory report:

- ▶ The variant affects a conserved residue located in a critical domain of the *APC* protein: the  $\beta$ -catenin binding domain. Despite the neutral effect predicted by *in silico* tools, the c.3920T>A nucleotide change affects an (A)3(T)(A)4 sequence element, converting it into an extended tract of eight adenosine nucleotides (A8).
- ▶ Known associated cancer risks are restricted, so far, to individuals of AJ descent as assessed by asking about the individual’s Jewish ancestry and the country of birth of, at least, the individual and his or her parents.
- ▶ In individuals of AJ descent, known cancer associated risk is limited to CRC. The variant does not increase the risk of polyposis, despite it being an *APC* variant.
- ▶ To date, there are not good quality data to suggest that risks of other cancer types and in other populations (non-Ashkenazi Jews and non-Jewish individuals) are greater than in the general population.
- ▶ Predictive testing of FDR is advised when the variant is detected in individuals of AJ descent.

### CONCLUSIONS

The aim of this document is to summarise the evidence on the prevalence of the *APC* I1307K allele in different populations and the associated risk for cancer. This evidence has been used to provide recommendations on the laboratory classification of the variant, define the role of predictive testing for I1307K and suggest recommendations for cancer screening in I1307K heterozygous and homozygous individuals. See summary box for an executive summary of the recommendations proposed.

### SUMMARY BOX

- ⇒ The assessment of Ashkenazi Jewish (AJ) descent in clinical practice should include the individual’s Jewish ancestry, and the country of birth of, at least, the individual and parents.
- ⇒ I1307K is a risk factor for colorectal cancer (CRC) in AJ individuals; it should be evaluated in this subpopulation.
- ⇒ I1307K should be classified as ‘pathogenic, low penetrance’. In this document, we propose some information that may be added to laboratory reports.
- ⇒ I1307K heterozygous and homozygous individuals of AJ origin should undergo colonoscopy screening every 5 years, starting at age 45–50 years.
- ⇒ We recommend predictive testing for I1307K in first-degree relatives (FDRs) in AJ families, and in second-degree relatives when FDRs are not tested. When genetic testing is not available for relatives, current recommendations for individuals with an FDR affected with CRC may be advised.
- ⇒ To date, there are not enough good quality data to consider I1307K as a risk factor for CRC in non-AJ Jewish and in non-Jewish individuals and as a risk factor for extracolonic cancers. Individuals of non-AJ descent harbouring I1307K should be enrolled in their corresponding national CRC screening programmes.

### RECOMMENDATIONS FOR FUTURE RESEARCH BASED ON THE IDENTIFIED KNOWLEDGE GAPS

- ▶ Historically, studies have relied on self-reported AJ ancestry. The term ancestry may have variable interpretations,<sup>57</sup> resulting in potential misinterpretation when comparing across studies and/or translating research data into the clinical setting.<sup>58</sup> Therefore, we strongly recommend determining AJ and non-AJ ancestries by using genomic/genetic markers. This will confirm or rule out a common origin of I1307K worldwide and provide more accurate assessments of I1307K-associated risks. Also, this will likely result in the definition of AJ-associated genetic markers or criteria that improve ancestry definition in the context of genetic counselling for I1307K heterozygotes or homozygotes. In the meanwhile, prospective studies evaluating CRC and other cancer types in large cohorts (preferably geographically matched case–control studies) are required to robustly confirm or rule out the increased CRC or extracolonic cancer risk in non-AJ I1307K heterozygotes or homozygotes. Also, we encourage the publication of available data to determine whether the I1307K allele confers increased risk of extracolonic cancers in AJ individuals.
- ▶ Should the cancer risk associated with I1307K prove to be different in different populations, regardless of the common or diverse origin of the allele, it may be hypothesised that different populations harbour other genetic variants that act in concert with I1307K, modulating the (colorectal) cancer risk associated with I1307K. The analysis of genetic and non-genetic CRC risk factors will likely refine CRC risk estimations in I1307K individuals, thus determining the future clinical management of I1307K heterozygous and homozygous individuals.
- ▶ The generation of further, robust experimental data and the analysis of sequencing data obtained from tumours developed by individuals with the I1307K variant are encouraged to produce convincing evidence on the underlying mechanism of action of the allele. In particular, somatic mutation analysis of the A(8) sequence around the *APC* c.3920T>A

variant in tumours should shed light into the mechanism of pathogenicity.

#### Author affiliations

- <sup>1</sup>Hereditary Cancer Programme, Catalan Institute of Oncology, Hospitalet de Llobregat, Barcelona, Spain  
<sup>2</sup>Oncobell Programme, IDIBELL, Hospitalet de Llobregat, Barcelona, Spain  
<sup>3</sup>Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain  
<sup>4</sup>Department of Gastroenterology and Hepatology, Hadassah Medical Center, Hebrew University of Jerusalem, Jerusalem, Israel  
<sup>5</sup>The Polyposis Registry, St Mark's Hospital, London North West University Healthcare NHS Trust, Harrow, UK  
<sup>6</sup>Department of Surgery and Cancer, Imperial College, London, UK  
<sup>7</sup>Catalan Cancer Plan, Department of Health of Catalonia, Barcelona, Spain  
<sup>8</sup>Oncology Data Analytics Programme, Catalan Institute of Oncology, Hospitalet de Llobregat, Barcelona, Spain  
<sup>9</sup>Department of Clinical Sciences, Faculty of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain  
<sup>10</sup>Universitat de Barcelona Institute of Complex System (UBICS), University of Barcelona, Barcelona, Spain  
<sup>11</sup>Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain  
<sup>12</sup>Inherited Tumour Syndromes Research Group, Cardiff University, Cardiff, Wales, UK  
<sup>13</sup>Sanford R. Weiss MD Center for Hereditary Colorectal Neoplasia, Cleveland Clinic, Cleveland, Ohio, USA

**Twitter** Laura Valle @LValleResearch, Andrew Latchford @AndyLatchford, Pilar Mur @PilarMurM, Ian M Frayling @Doctor\_IMF, Brandie Heald @bhealdleach and on behalf of the InSIGHT Council @insightmeeting

**Contributors** GC, IMF, AL, BH and LK conceived the study. LV, AL, BH and PM performed the review of the literature. PM, VM and LV carried out the statistical analyses. GC, IMF, AL, BH, LK and LV were involved in the design of the study and intellectual discussions that led to the recommendations. All authors were involved in the interpretation of data and in writing and critically reviewing the manuscript. Author acting as guarantor: GC.

**Funding** This study was funded by the International Society for Gastrointestinal Hereditary Tumours (InSIGHT); Spanish Ministry of Science and Innovation (Agencia Estatal de Investigación), co-funded by FEDER funds -a way to build Europe- [PID2019-111254RB-I00 and PID2020-112595RB-I00]; Instituto de Salud Carlos III [CIBERONC CB16/12/00234]; and Government of Catalonia [AGAUR 2021\_SGR\_01112, and CERCA Program for institutional support].

**Competing interests** BH is an employee and shareholder of Invitae Corp.

**Patient consent for publication** Not applicable.

**Ethics approval** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** All data relevant to the study are included in the article or uploaded as supplementary information.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

#### ORCID iDs

Laura Valle <http://orcid.org/0000-0003-0371-0844>  
 Andrew Latchford <http://orcid.org/0000-0002-8626-188X>  
 Pilar Mur <http://orcid.org/0000-0003-0780-926X>  
 Victor Moreno <http://orcid.org/0000-0002-2818-5487>  
 Ian M Frayling <http://orcid.org/0000-0002-3420-0794>  
 Brandie Heald <http://orcid.org/0000-0003-4227-3675>  
 Gabriel Capellá <http://orcid.org/0000-0002-4669-7320>

#### REFERENCES

- Kopanos C, Tsiolkas V, Kouris A, et al. VarSome: the human genomic variant search engine. *Bioinformatics* 2019;35:1978–80.
- Azzopardi D, Dallosso AR, Eliason K, et al. Multiple rare nonsynonymous variants in the adenomatous polyposis coli gene predispose to colorectal adenomas. *Cancer Res* 2008;68:358–63.
- Laken SJ, Petersen GM, Gruber SB, et al. Familial colorectal cancer in Ashkenazim due to a hypermutable tract in APC. *Nat Genet* 1997;17:79–83.
- Gryfe R, Di Nicola N, Gallinger S, et al. Somatic instability of the APC I1307K allele in colorectal neoplasia. *Cancer Res* 1998;58:4040–3.
- Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of medical genetics and genomics and the association for molecular pathology. *Genet Med* 2015;17:405–24.
- Boursi B, Sella T, Liberman E, et al. The APC p.I1307K polymorphism is a significant risk factor for CRC in average risk Ashkenazi jews. *Eur J Cancer* 2013;49:3680–5.
- Rozen P, Shomrat R, Strul H, et al. Prevalence of the I1307K APC gene variant in Israeli Jews of differing ethnic origin and risk for colorectal cancer. *Gastroenterology* 1999;116:54–7.
- Karczewski KJ, Francioli LC, Tiao G, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature* 2020;581:434–43.
- Prior TW, Chadwick RB, Papp AC, et al. The I1307K polymorphism of the APC gene in colorectal cancer. *Gastroenterology* 1999;116:58–63.
- Forkosh E, Bergel M, Hatchell KE, et al. Ashkenazi Jewish and other white APC I1307K carriers are at higher risk for multiple cancers. *Cancers* 2022;14:5875.
- Niell BL, Long JC, Rennert G, et al. Genetic anthropology of the colorectal cancer-susceptibility allele APC I1307K: evidence of genetic drift within the Ashkenazim. *Am J Hum Genet* 2003;73:1250–60.
- Greenwood CMT, Sun S, Veenstra J, et al. How old is this mutation?—A study of three Ashkenazi Jewish founder mutations. *BMC Genet* 2010;11:39.
- Peña-Chilet M, Roldán G, Perez-Florido J, et al. CSVS, a crowdsourcing database of the Spanish population genetic variability. *Nucleic Acids Res* 2021;49:D1130–7.
- Ameur A, Dahlberg J, Olason P, et al. SweGen: a whole-genome data resource of genetic variability in a cross-section of the Swedish population. *Eur J Hum Genet* 2017;25:1253–60.
- Alonso-Molero J, Molina AJ, Jiménez-Moleón JJ, et al. Cohort profile: the MCC-spain follow-up on colorectal, breast and prostate cancers: study design and initial results. *BMJ Open* 2019;9:e031904.
- Smith D, Burr E. *Understanding world religions: a road map for justice and peace*. 2nd ed. New York: Rowman & Littlefield, 2014.
- Mosk C. *Nationalism and economic development in modern eurasia*. 1st ed. London: Routledge, 2013.
- Ben-Sasson HH. Germany. In: Berenbaum M, Skolnik F, eds. *Encyclopaedia Judaica*. 2nd ed. Detroit: Macmillan Reference, 2007: 524.
- Need AC, Kasperaviciute D, Cirulli ET, et al. A genome-wide genetic signature of Jewish ancestry perfectly separates individuals with and without full Jewish ancestry in a large random sample of European Americans. *Genome Biol* 2009;10:R7.
- Olshen AB, Gold B, Lohmueller KE, et al. Analysis of genetic variation in Ashkenazi Jews by high density SNP genotyping. *BMC Genet* 2008;9:14.
- Kenny EE, Pe'er I, Karban A, et al. A genome-wide scan of Ashkenazi Jewish Crohn's disease suggests novel susceptibility loci. *PLoS Genet* 2012;8:e1002559.
- Thomas MG, Weale ME, Jones AL, et al. Founding mothers of Jewish communities: geographically separated Jewish groups were independently founded by very few female ancestors. *Am J Hum Genet* 2002;70:1411–20.
- Ostrer H. A genetic profile of contemporary Jewish populations. *Nat Rev Genet* 2001;2:891–8.
- Behar DM, Metspalu E, Kivisild T, et al. The matrilineal ancestry of Ashkenazi jewry: portrait of a recent founder event. *Am J Hum Genet* 2006;78:487–97.
- Behar DM, Garrigan D, Kaplan ME, et al. Contrasting patterns of Y chromosome variation in Ashkenazi Jewish and host non-Jewish European populations. *Hum Genet* 2004;114:354–65.
- Rozen P, Naiman T, Strul H, et al. Clinical and screening implications of the I1307K adenomatous polyposis coli gene variant in Israeli Ashkenazi Jews with familial colorectal neoplasia. Evidence for a founder effect. *Cancer* 2002;94:2561–8.
- Drucker L, Shpilberg O, Neumann A, et al. Adenomatous polyposis coli I1307K mutation in Jewish patients with different ethnicity: prevalence and phenotype. *Cancer* 2000;88:755–60.
- Stern HS, Viertelhausen S, Hunter AG, et al. APC I1307K increases risk of transition from polyp to colorectal carcinoma in Ashkenazi Jews. *Gastroenterology* 2001;120:392–400.
- Locker GY, Kaul K, Weinberg DS, et al. The I1307K APC polymorphism in Ashkenazi Jews with colorectal cancer: clinical and pathologic features. *Cancer Genet Cytogenet* 2006;169:33–8.
- Woodage T, King SM, Wacholder S, et al. The APC I1307K allele and cancer risk in a community-based study of Ashkenazi Jews. *Nat Genet* 1998;20:62–5.



- 31 Shtoyerman-Chen R, Friedman E, Figer A, *et al.* The I1307K APC polymorphism: prevalence in non-Ashkenazi Jews and evidence for a founder effect. *Genet Test* 2001;5:141–6.
- 32 Figer A, Shtoyerman-Chen R, Tamir A, *et al.* Phenotypic characteristics of colo-rectal cancer in I1307K APC germline mutation carriers compared with sporadic cases. *Br J Cancer* 2001;85:1368–71.
- 33 Fidler HH, Figer A, Geva R, *et al.* Genetic analyses in consecutive Israeli Jewish colorectal cancer patients. *Am J Gastroenterol* 2005;100:1376–80.
- 34 Zauber NP, Sabbath-Solitare M, Marotta S, *et al.* Clinical and genetic findings in an Ashkenazi Jewish population with colorectal neoplasms. *Cancer* 2005;104:719–29.
- 35 Ukaegbu C, Levi Z, Fehlmann TD, *et al.* Characterizing germline APC and MUTYH variants in Ashkenazi Jews compared to other individuals. *Fam Cancer* 2021;20:111–6.
- 36 Teo E B. *Sephardi. Encyclopedia britannica.* 2022.
- 37 Gryfe R, Di Nicola N, Lal G, *et al.* Inherited colorectal polyposis and cancer risk of the APC I1307K polymorphism. *Am J Hum Genet* 1999;64:378–84.
- 38 Strul H, Barenboim E, Leshno M, *et al.* The I1307K adenomatous polyposis coli gene variant does not contribute in the assessment of the risk for colorectal cancer in Ashkenazi Jews. *Cancer Epidemiol Biomarkers Prev* 2003;12:1012–5.
- 39 Syngal S, Schrag D, Falchuk M, *et al.* Phenotypic characteristics associated with the APC gene I1307K mutation in Ashkenazi Jewish patients with colorectal polyps. *JAMA* 2000;284:857–60.
- 40 Lamlum H, Al Tassan N, Jaeger E, *et al.* Germline APC variants in patients with multiple colorectal adenomas, with evidence for the particular importance of E1317Q. *Hum Mol Genet* 2000;9:2215–21.
- 41 Michils G, Tejpar S, Fryns J-P, *et al.* Pathogenic mutations and rare variants of the APC gene identified in 75 Belgian patients with familial adenomatous polyposis by fluorescent enzymatic mutation detection (EMD). *Eur J Hum Genet* 2002;10:505–10.
- 42 Rennert G, Almog R, Tomsho LP, *et al.* Colorectal polyps in carriers of the APC I1307K polymorphism. *Dis Colon Rectum* 2005;48:2317–21.
- 43 Gershoni-Baruch R, Patael Y, *et al.* Dagan. Association of the I1307K APC mutation with hereditary and sporadic breast/ovarian cancer: more questions than answers. *Br J Cancer* 2000;83:153–5.
- 44 Redston M, Nathanson KL, Yuan ZQ, *et al.* The APC I1307K allele and breast cancer risk. *Nat Genet* 1998;20:13–4.
- 45 Leshno A, Shapira S, Liberman E, *et al.* The APC I1307K allele conveys a significant increased risk for cancer. *Int J Cancer* 2016;138:1361–7.
- 46 Poynter JN, Cooney KA, Bonner JD, *et al.* APC I1307K and the risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2006;15:468–73.
- 47 Lehrer S, McCurdy LD, Stock RG, *et al.* Body mass, age, and the APC I1307K allele in Ashkenazi Jewish prostate cancer patients. *Cancer Genet Cytogenet* 2000;122:131–3.
- 48 Lehrer S, Diamond EJ, Stone NN, *et al.* Elevated serum triiodothyronine (t3) in Ashkenazi Jewish prostate cancer patients carrying the i1307k allele of the APC (adenomatous polyposis coli) gene. *Urol Oncol* 2003;21:101–4.
- 49 Liberman E, Kraus S, Sagiv E, *et al.* The APC E1317Q and I1307K polymorphisms in non-colorectal cancers. *Biomed Pharmacother* 2007;61:566–9.
- 50 Shamai S, Nabiochtchikov I, Kraus S, *et al.* CD24 and APC genetic polymorphisms in pancreatic cancers as potential biomarkers for clinical outcome. *PLoS One* 2015;10:e0134469.
- 51 Abdel-Malak C, Darwish H, Elsaid A, *et al.* Association of APC I1307K and E1317Q polymorphisms with colorectal cancer among Egyptian subjects. *Fam Cancer* 2016;15:49–56.
- 52 Zauber P, Sabbath-Solitare M, Stephen PM, *et al.* Sporadic desmoid tumor in an Ashkenazi patient homozygous for the APC\*1307K gene mutation. *Acta Oncol* 2008;47:1158–61.
- 53 Rosenblum A, Springer M, Eppolito A, *et al.* Homozygous germline APC p.I1307K variants: a case series. *Case Rep Oncol* 2021;14:1295–303.
- 54 Roos VH, Mangas-Sanjuan C, Rodriguez-Gironde M, *et al.* Effects of family history on relative and absolute risks for colorectal cancer: a systematic review and meta-analysis. *Clinical Gastroenterology and Hepatology* 2019;17:2657–2667.
- 55 Breen KE, Katona BW, Catchings A, *et al.* An updated counseling framework for moderate-penetrance colorectal cancer susceptibility genes. *Genet Med* 2022;24:2587–90.
- 56 Ma X, Zhang B, Zheng W. Genetic variants associated with colorectal cancer risk: comprehensive research synopsis, meta-analysis, and epidemiological evidence. *Gut* 2014;63:326–36.
- 57 Royal CD, Novembre J, Fullerton SM, *et al.* Inferring genetic ancestry: opportunities, challenges, and implications. *Am J Hum Genet* 2010;86:661–73.
- 58 Jorde LB, Bamshad MJ. Genetic ancestry testing: what is it and why is it important? *JAMA* 2020;323:1089–90.
- 59 Figer A, Irmin L, Geva R, *et al.* Genetic analysis of the APC gene regions involved in attenuated APC phenotype in Israeli patients with early onset and familial colorectal cancer. *Br J Cancer* 2001;85:523–6.
- 60 Goldberg Y, Barnes-Kedar I, Lerer I, *et al.* Genetic features of Lynch syndrome in the Israeli population. *Clin Genet* 2015;87:549–53.
- 61 Zauber NP, Sabbath-Solitare M, Marotta SP, *et al.* The characterization of somatic APC mutations in colonic adenomas and carcinomas in Ashkenazi Jews with the APC I1307K variant using linkage disequilibrium. *J Pathol* 2003;199:146–51.
- 62 Lothe RA, Hektoen M, Johnsen H, *et al.* The APC gene I1307K variant is rare in Norwegian patients with familial and sporadic colorectal or breast cancer. *Cancer Res* 1998;58:2923–4.
- 63 Evertsson S, Lindblom A, Sun XF. APC I1307K and E1317Q variants are rare or do not occur in Swedish colorectal cancer patients. *Eur J Cancer* 2001;37:499–502.
- 64 Kapitanović S, Cacev T, Radosević S, *et al.* APC gene loss of heterozygosity, mutations, E1317Q, and I1307K germ-line variants in sporadic colon cancer in Croatia. *Exp Mol Pathol* 2004;77:193–200.
- 65 Zhou X-L, Eriksson U, Werelius B, *et al.* Definition of candidate low risk APC alleles in a Swedish population. *Int J Cancer* 2004;110:550–7.
- 66 Chen-Shtoyerman R, Theodor L, Harmati E, *et al.* Genetic analysis of familial colorectal cancer in Israeli Arabs. *Hum Mutat* 2003;21:446–7.
- 67 Bougateg K, Marrakchi R, Ouerhani S, *et al.* No evidence of the APC D1822V missense variant's pathogenicity in Tunisian patients with sporadic colorectal cancer. *Pathol Biol (Paris)* 2009;57:e67–71.
- 68 Akcay IM, Celik E, Agaoglu NB, *et al.* Germline pathogenic variant spectrum in 25 cancer susceptibility genes in Turkish breast and colorectal cancer patients and elderly controls. *Int J Cancer* 2021;148:285–95.
- 69 Dunder M, Caglayan AO, Saatci C, *et al.* How the I1307K adenomatous polyposis coli gene variant contributes in the assessment of risk of colorectal cancer, but not stomach cancer, in a Turkish population. *Cancer Genet Cytogenet* 2007;177:95–7.
- 70 Guo J, Lim R, Soo R, *et al.* APC I1307K and the E1317Q variants are not present in Chinese colorectal cancer patients. *Genet Med* 2004;6:237–8.