APC

The *APC* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary roles of *APC* are to help control how often a cell divides and how cells move and attach to other cells in the body.

Like most genes, each person has two copies of the *APC* gene: one inherited from each parent. A mutation in a single *APC* gene inherited from either parent is known to cause Familial Adenomatous Polyposis (FAP) or Attenuated Familial Adenomatous Polyposis (AFAP). *APC* mutations are associated with an increased risk of polyposis (a large number of polyps in the gastrointestinal tract) as well as colorectal and other cancers.

The difference between FAP and AFAP is primarily the clinical symptoms, such as the age at which colorectal polyps first appear and the total number of colon polyps that develop. In general, individuals with FAP develop more polyps and have higher cancer risks at earlier ages.

Individuals with FAP and AFAP also have increased risks of other cancers such as brain (medulloblastoma), liver (especially a type called hepatoblastoma that only occurs in children younger than age 5), pancreatic, small bowel (duodenal), stomach, and thyroid. Non-cancerous features of FAP and AFAP can include: osteomas (bone tumors, usually in the skull or jaw bone); desmoid tumors (growths, usually in the abdomen); adrenal gland masses; dental abnormalities (such as extra or missing teeth); skin growths (such as cysts or fibromas); and pigmented regions on the retina of the eye referred to as congenital hypertrophy of the retinal pigment epithelium (CHRPE). These non-cancerous findings are also more common in individuals with FAP compared to AFAP.[2]

Approximately 20 to 25% of individuals with *APC* mutations are the first in their family to carry the mutation.[1,2] This is referred to as a “de novo” mutation. Individuals with de novo mutations have the same cancer risks as those with an inherited mutation from a parent and have a 50% chance of passing the mutation on to their children.

How common are mutations in the *APC* gene?

Mutations in the *APC* gene are rare—found in approximately 3 in 10,000 individuals in a study of the United Kingdom population.[3] *APC* mutations account for <1% of all colorectal cancers.[1]

[1] Jasperson KW, Tuohy TM, Neklason DW, Burt RW. Hereditary and familial colon cancer. *Gastro*. 2010 Jun;138(6):2044-58.
[2] Bisgaard ML, Fenger K, Bulow S, Niebuhr E, Mohr J. Familial adenomatous polyposis (FAP): frequency, penetrance, and mutation rate. *Hum Mutat*. 1994;3:121–5.
[3] Burn J, Chapman P, Delhanty J et al. The UK Northern region genetic register for familial adenomatous polyposis coli: use of age of onset, congenital hypertrophy of the retinal pigment epithelium, and DNA markers in risk calculations. *Journal of Medical Genetics*. 1991;28(5):289-296.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *APC* gene, her chances of developing colorectal and other cancers, including brain (medulloblastoma), pancreatic, small bowel (duodenal), stomach, and thyroid, as well as non-cancerous growths called desmoid tumors, are greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

Cancer by age 80	Average US woman[4]	With *APC* mutation
Colorectal	2.8%	70-100%[1,5]
Brain (medulloblastoma)	<1%	Elevated[6]
Desmoid tumors	<0.1%[7]	Elevated[8]
Pancreatic	<1%	1.7%[9]
Small bowel (duodenal)	<1%	Elevated[10]
Stomach	<1%	Elevated][1]
Thyroid	1.6%	2.1%[9]

Elevated: Risk is increased, but further research may clarify the exact risk figure.

Men

If a man has a mutation in the *APC* gene, his chances of developing colorectal and other cancers, including brain (medulloblastoma), pancreatic, small bowel (duodenal), stomach, and thyroid, as well as non-cancerous growths called desmoid tumors, are greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

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[4] Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2010-2012. DevCan software (http://surveillance.cancer.gov/devcan) V 6.7.0, Accessed June 2015.
[5] Burt RW, et al. Genetic testing and phenotype in a large kindred with attenuated familial adenomatous polyposis. *Gastro*. 2004 Aug;127(2):444-51.
[6] Attard TM, Giglio P, Koppula S, Snyder C, Lynch HT. Brain tumors in individuals with familial adenomatous polyposis: a cancer registry experience and pooled case report analysis. *Cancer*. 2007;109(4):761-6.
[7] Bhandari S, Sinha A, Clark SK. Evaluation of management of desmoids tumours associated with familial adenomatous polyposis in Dutch patients. *Br J Cancer*. 2011;104(7):1236.
[8] Sturt NJ, Gallagher MC, Bassett P, et al. Evidence for genetic predisposition to desmoid tumours in familial adenomatous polyposis independent of the germline APC mutation. *Gut*. 2004;53(12):1832-6.
[9] Giardiello FM, Offerhaus GJ, Lee DH, et al. Increased risk of thyroid and pancreatic carcinoma in familial adenomatous polyposis. *Gut*. 1993;34(10):1394-6.
[10] Bülow S, Björk J, Christensen IJ, et al. Duodenal adenomatosis in familial adenomatous polyposis. *Gut*. 2004;53(3):381-6.

Cancer by age 80	Average US man[4]	With *APC* mutation
Colorectal	3.4%	70-100%[1,5]
Brain (medulloblastoma)	<1%	Elevated[6]
Desmoid tumors	<0.1[7]	Elevated[8]
Pancreatic	1%	1.7%[9]
Small bowel (duodenal)	<1%	Elevated[10]
Stomach	<1%	Elevated[1]
Thyroid	<1%	2.1%[9]

Elevated: Risk is increased, but further research may clarify the exact risk figure.

Additional information

Not all *APC* mutations have the same impact on cancer risk.

A specific mutation in the *APC* gene, called I1307K, is not associated with FAP or AFAP, but is linked to a slightly increased risk to develop colorectal cancer. Research on this specific gene mutation is ongoing. Studies have shown approximately 5-10% of all people of Ashkenazi Jewish descent carry this mutation, and the current colorectal cancer risk estimate for *APC* I1307K is based on studies in this specific population.[11,12]

Screening guidelines (FAP and AFAP)

Below is a summary of screening guidelines from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) established by experts at the National Comprehensive Cancer Network (NCCN).[13] They are for individuals with FAP or AFAP who have a mutation in the *APC* gene. If you have a mutation in this gene, your healthcare provider may use these NCCN Guidelines® to help create a customized screening plan for you.

[11] 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. *Gastro*. January 1999;116(1):54-7.
[12] 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*. November 2013;49(17):3680-5.
[13] Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Colorectal. V.2.2016. © National Comprehensive Cancer Network, Inc 2016. All rights reserved. Accessed October 26, 2016. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

Women and Men

Colorectal cancer (FAP)[14]

- Starting at age 10-15: Flexible sigmoidoscopy or colonoscopy every year.
- Starting at age 18 or depending on number of polyps: NCCN recommends colectomy (surgical removal of the colon).
- Following colectomy: Speak to your provider about recommended follow up, which may include surveillance with endoscopy, and medications to reduce the risks of polyps and cancer.

Colorectal cancer (AFAP)[14]

- In late teens: Colonoscopy every 2-3 years until polyps are found. After polyps are found, colonoscopy every 1-2 years.
- Depending on age and number of polyps: NCCN recommends colectomy (surgical removal of the colon).
- Following colectomy: Speak to your provider about recommended follow up, which may include surveillance with endoscopy, and medications to reduce the risk of polyps and cancer.

Brain cancer (medulloblastoma) (FAP, AFAP)[14]

- Physical examination every year.

Desmoid tumors (FAP)[14]

- Abdominal palpation every year.
- **With family history or symptoms of desmoid tumors:** Your provider may discuss abdominal MRI or CT 1-3 years after colectomy and then every 5-10 years.

Pancreatic cancer (FAP, AFAP)

- Currently, there are no pancreatic cancer screening guidelines from the NCCN specific to *APC* mutation carriers. Your provider may discuss screening or referral to a specialist.

Small bowel cancer (duodenal and other sections) (FAP, AFAP)[14]

- **Starting at age 20-25 years, or earlier if colectomy before age 20:** Upper endoscopy (including complete visualization of ampulla of Vater). Frequency of the endoscopy depends on the number and size of polyps identified.

Stomach cancer (FAP, AFAP)[14]

- **Starting at age 20-25 years:** Examine stomach at the time of upper endoscopy.
- Surgery may be recommended based on findings of biopsy.

[14] National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal. NCCN Guidelines Version 2.2016. Available at www.nccn.org. Published September 2016.

Thyroid cancer (FAP, AFAP)[14]

- **Starting in late teenage years:** Thyroid examination every year. Your provider may discuss a thyroid ultrasound every year.

Screening guidelines (APC I1307K)

Below is a summary of screening guidelines from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) established by experts at the National Comprehensive Cancer Network (NCCN).[13] They are for individuals who have an *APC* I1307K mutation. If you have this mutation, your healthcare provider may use these NCCN Guidelines® to help create a customized screening plan for you.

Women and Men

Colorectal cancer[14]

- **Beginning at age 40 or 10 years younger than the earliest diagnosis of colorectal cancer in a parent, sibling, or child (whichever is earlier):** Colonoscopy every 5 years.
- These recommendations may change if you have polyps, colorectal cancer, inflammatory bowel disease (IBD), or family history of colorectal cancer.

Useful resources

Colon Cancer Alliance

An organization dedicated to colon cancer prevention, funding colon cancer research and providing support to patients.
www.ccalliance.org

Hereditary Colon Cancer Foundation

A nonprofit organization serving the hereditary colorectal cancer community.
www.hcctakesguts.org

Kintalk

An educational and family communication site for individuals and their families with hereditary cancer conditions
www.kintalk.org

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