Familial adenomatous polyposis (also called FAP) is caused by pathogenic (or harmful) variants in the APC gene. FAP is typically characterized by a person developing more than 100 but usually less than 1000 colon polyps within their lifetime, putting them at a very high risk of early onset colon cancer (under age 50). In addition to colon polyps, individuals with FAP are more susceptible to develop some rarer medical conditions:

- Polyps in the stomach or the small bowel
- Desmoids (tumors of fibrous connective tissue)
- Osteomas (benign tumors of the bone, often on the skull)
- Having more teeth than usual (supernumerary teeth)
- Benign freckling on the retina of the eye, called CHRPE

Colon cancer is the main concern for individuals with FAP, however research has shown that there is a small but increased chance to develop other cancers:

Papillary cancer of the thyroid	Less than 2% chance
Hepatoblastoma (pediatric liver cancer)	1-2% chance
Pancreatic cancer	Less than 1% chance
Stomach cancer	Less than 1% chance
Duodenal/intestinal cancer	4-12% chance

Sometimes individuals with a pathogenic variant in the APC gene develop many polyps (10-100 polyps) but not over 100 polyps that individuals with FAP typically will have. These individuals are considered to have **Attenuated Familial Adenomatous Polyposis (or AFAP).** Those with AFAP are still at high risk of colon cancer, but this risk is lower and often later onset (after age 50) than in those with classic FAP. Similar to classic FAP, those with AFAP are also at increased risk of polyps in the stomach or small intestine, thyroid cancer, and duodenal/intestinal cancer; however the rarer features of FAP (CHRPE, desmoid tumors) are much less common in AFAP.

HOW DOES FAP RUN IN FAMILIES?

FAP and AFAP are both are inherited in an autosomal dominant pattern, meaning that children of someone who carries a pathogenic variant each have a 50% risk to inherit the variant and associated cancer risks. Women and men have the same chances to inherit and pass down variants in these genes, therefore both sides of the family are important to look at when trying to determine if someone has a higher chance to have FAP or AFAP.

FAP and AFAP can both run in families; however, about 30% of the time an individual with FAP is the first one in the family to have the condition due to random chance (called “de novo”). Those with a new diagnosis of FAP or AFAP in a family can still pass it on to future generations.

GENETIC TESTING FOR FAP/AFAP

Genetic testing for pathogenic variants that cause FAP/AFAP has been available for many years, and the testing methods have changed and improved over time. There are several different ways to approach to testing in these genes, depending on the history and any prior testing that may have been done. Different approaches include:

- *Single site analysis*: Testing specific to a known pathogenic variant in the family
- *Full gene sequencing and rearrangement analysis*: Comprehensive testing to search for all currently detectable variants in the APC gene.
- *Gene panels*: Newer, more broadly based gene tests that would include not only the APC gene, but other genes known or suspected to be associated with colon polyps and increased cancer risks

WHO SHOULD BE OFFERED TESTING FOR FAP?

The National Comprehensive Cancer Network (NCCN) is a group of medical professionals that regularly meet to look over any updates in research studies and determine recommendations for who should be considered at a higher risk for one of these gene mutations, and thus should be offered genetic testing.

- Individuals with a personal history of at least 20 colon polyps (specifically adenomatous ones) in their lifetime
- Individuals with a family history of a known APC pathogenic variant in a relative
- Testing can be considered if a person has only developed 10-20 colon polyps in their lifetime especially if these were early onset (under age 50) or there is a strong family history of colon polyps
- Testing can be carefully considered in those with a desmoid tumor, hepatoblastoma, a specific type of thyroid cancer called cribiform-morular papillary thyroid cancer, or with CHRPE that is multifocal or present in both eyes

Those who undergo testing for the APC gene due to a personal history of many colon polyps should also be offered testing for another genetic predisposition to colon polyps called MUTYH-associated polyposis (MAP). These two conditions are caused by separate genetic

variants but it is often difficult to distinguish between them without genetic testing.

COLONIC POLYPOSIS OF UNKNOWN ETIOLOGY (CPUE)

It is fairly common for individuals to have negative or inconclusive genetic testing for FAP despite having developed many colon polyps. It is likely that researchers have not yet discovered all of the genes or other factors that can cause someone to develop colon polyps. If someone has developed at least 20 colon polyps (adenomatous type) in their lifetime but their genetic testing does not show that they have a genetic variant, they are designated to have colonic polyposis of unknown etiology (CPUE).

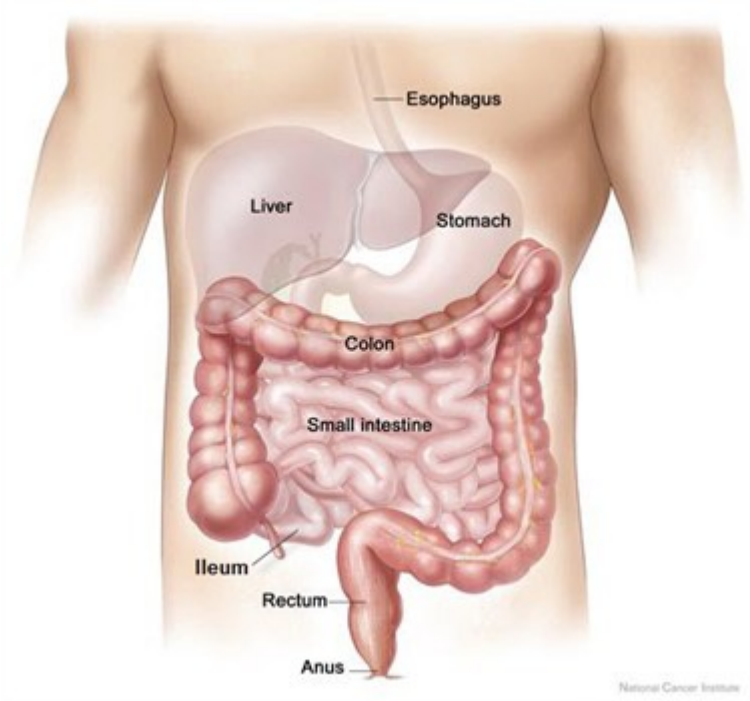
Even though they do not have FAP or another genetic cause of their polyps, individuals with CPUE should still have close surveillance for future colon polyps. This includes a colonoscopy every 1-2 years to remove any new polyps as they appear.

Close family members of those who have CPUE do not need genetic testing but should also undergo close surveillance starting at least at age 40 (or younger if there is early onset colon polyps or colon cancer in the family). This includes colonoscopies at least every 3-5 years, but maybe more frequent if the individual with CPUE has had more than 100 polyps removed or if the family member has polyps found on their own colonoscopy. A discussion with a genetic counselor and/or a high-risk gastrointestinal screening specialist can help determine what is recommended specifically for you and your family members.

CANCER SCREENING AND RISK MANAGEMENT FOR FAP AND AFAP

If you are tested and found to have FAP or AFAP, it is recommended to discuss your management plan with your healthcare team, and if available, to seek consultation through a specialized high-risk clinic. General recommendations are included here based on the updated guidelines of the (NCCN), but may be tailored to your specific medical and family history.

All individuals with FAP and AFAP should have a **colonoscopy at least every year** to remove new colon polyps which may grow into colorectal cancer. This screening should **start around age 10-15** because polyps can start to grow even at a young age. The good news is that this screening for colon cancer is highly effective in reducing the chance that someone would develop colon cancer and reduces the severity of colon cancer.



Source: MTLSD.
https://sites.google.com/a/mtlstudents.net/digestive-system_riley_williams/home/4-small-in/ileum

On the other hand, if polyps become too numerous to remove successfully, a physician will likely recommend removing the colon (colectomy). Patients should be carefully counseled about the risks, disadvantages, and benefits of the various options for colectomy. Individuals with FAP who have had a colectomy will still require regular follow up with their gastrointestinal providers to check for polyps that could develop in the ileum (last section of the small intestine) and/or the rectum.

An upper endoscopy (EGD) to look at the stomach, duodenum (the first part of the small intestine immediately beyond the stomach), and ampulla of Vater (a dilated part of the duodenum) should be completed every 4 years starting at age 20-25 years. This should be repeated more frequently if adenomatous polyps are present.

Individuals with FAP should have an annual thyroid examination starting in the late teens. They should also have an annual physical with their physician that includes a neurological exam and a physical exam of the abdomen to check for desmoid tumors. CT or MRI imaging of the abdomen could be considered if there is a family history of desmoid tumors.

In families with FAP and a history of pancreatic cancer, individualized screening may be offered based on the history, but no specific guidelines currently exist.

Click here to learn more about scheduling a genetic counseling appointment for questions about hereditary cancer predisposition.