Ohio State University James Cancer Hospital and Solove Research Institute

FAMILIAL ADENOMATOUS POLYPOSIS

How common is colorectal cancer?

Colorectal cancer, which includes colon and rectal cancers, is one of the three most common cancers in the United States. Approximately 145,000 people are diagnosed with colorectal cancer every year. The lifetime risk for developing colorectal cancer in the general population is around 6 percent. It has been estimated that about 10 percent of all colorectal cancer cases are hereditary. This means the individual has inherited an increased likelihood for developing colorectal cancer.

What is familial adenomatous polyposis?

Familial adenomatous polyposis (FAP) is a hereditary colon cancer condition that affects about one in every 5,000–10,000 people, accounting for approximately 1 percent of colon cancer cases.

In families with FAP, people have an increased risk of developing adenomatous (precancerous) polyps throughout the colon. People with FAP usually develop at least 100 polyps and often have up to several thousand. The large number of polyps makes the chance of developing colon cancer nearly 100 percent, unless the colon is removed.

Individuals with FAP may also develop benign (non-cancerous) polyps of the upper stomach or fundus (the connection of the esophagus to the stomach), and adenomatous polyps of the lower stomach. They also have a slightly increased risk for cancer of the small intestine (duodenum), thyroid, pancreas, and brain. Children with FAP have an increased risk for hepatoblastoma, a type of liver cancer. Lastly, a benign eye condition known as congenital hypertrophy of the retinal pigment epithelium (CHRPE) is seen in individuals with FAP. CHRPEs are similar to freckles on the retina (the back of the eye) and do not hurt a person's eyesight.

What is Gardner Syndrome?

Some families with FAP have additional features that represent a variant of FAP known as **Gardner syndrome.** Individuals with Gardner syndrome may have benign skin changes such as fibromas (fibrous tumors), lipomas (fatty tumors), as well as soft tissue (desmoid) tumors of the abdominal wall. Desmoid tumors are found in 5-10 percent of patients with Gardner syndrome. Skin cysts, called epidermoid and sebaceous cysts, are seen in 66 percent of individuals with Gardner syndrome. Benign bone abnormalities (osteomas) can also be present, 90 percent of these are in the jaw but they also occur in the skull, fingers, toes and long bones. These tumors rarely turn into cancer, but they can cause both physical and cosmetic problems depending on where they occur and in some cases need to be removed. Dental abnormalities (extra, impacted, or unerupted teeth) my be seen in about one out of three individuals with Gardner syndrome. Lastly, congenital hypertrophy of the retinal pigment epithelium (CHRPE) is seen in 60-90 percent of individuals with Gardner syndrome.

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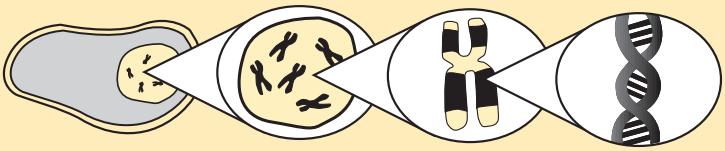
What is Attenduatd Familial Adenomatous Polyposis?

Another variant of FAP that is associated with the development of fewer polyps (between 10 and 100) and a later age of colon cancer diagnosis is called **Attenuated Familial Adenomatous Polyposis (AFAP).** Evidence suggests that desmoid tumors and CHRPE are rare or absent in individuals with AFAP.

How are FAP and its variants inherited?

Inherited information is contained in every cell in our body in structures called chromosomes. We have 46 chromosomes which come in pairs; 23 from our mother and 23 from our father. Each chromosome is made up of thousands of genes. Genes, like chromosomes, come in pairs. They are packages of genetic information (DNA) that act as instructions for making the substances that help our bodies function properly. An alteration in this genetic information can interfere with proper body functions by causing the gene to no longer work. These gene alterations are called mutations.



FAP and its variants, Gardner syndrome and AFAP, are caused by mutations (genetic damage) in the *APC* gene, which controls cell growth and division. FAP and AFAP can also be caused by mutations in the *MYH* gene. If there is a mutation in the *APC* or *MYH* genes, they can no longer control cell growth and division. For this reason, people with mutations in the *APC* or *MYH* genes have an increased risk for developing colorectal polyps and cancer.

What are the chances of inheriting an altered gene?

The *APC* gene is inherited in an "autosomal dominant" pattern. Autosomal means that both men and women can inherit an *APC* gene mutation. Dominant means that it takes only one *APC* gene mutation to have FAP (or one of its variants). All people have two copies of the *APC* gene, one from each parent. A person who has a parent with an *APC* mutation may inherit either that parent's *APC* gene with the mutation or that parent's working *APC* gene. Therefore, a person whose parent has an *APC* mutation has a 50-percent chance of inheriting the *APC* gene mutation and having FAP (or its variant). That person also has a 50 percent chance of not inheriting the *APC* gene mutation and would not have FAP. Their risk of cancer would be equal to the general population (average) risk of cancer.

The *MYH* gene is inherited in an "autosomal recessive" pattern. Recessive means that it takes two *MYH* gene mutations to cause FAP or AFAP, one from each parent. Individuals who carry one *MYH* mutation and one normal copy of the gene are called carriers. If two carriers have children together, there is a 25-percent chance that their child will inherit both nonworking copies, one from each parent, and thus have an increased risk for polyps and cancer. There is also a 50 percent chance that the child would inherit only one mutation (and also be a carrier) and a 25 percent chance that they would inherit both normal copies.

How are *APC* and *MYH* gene mutations detected?

It is possible to test for *APC* and *MYH* mutations using a blood sample. Once a mutation has been found in either the *APC* or *MYH* genes, the laboratory can look for that same mutation(s) in other family members (whether or not they have cancer) to see if they have inherited FAP or AFAP.

What if testing does not detect an altered *APC* of *MYH* gene?

Negative results (meaning an *APC* or *MYH* mutation is not found) can mean several things. First, it might mean that there is an *APC* or *APC* gene mutation that cannot be located by current testing methods. At least 10-35 percent of patients who meet FAP diagnostic criteria (more than 100 colonic adenomas) will NOT have a mutation detected in the *APC* gene when genetic testing is done. Even fewer AFAP families are found to have *APC* or *MYH* mutations. This is a limitation of many genetic tests. A negative test result could also mean that a different gene is responsible for the cancers or medical problems in the family. It is also possible that the polyps or cancers in the family are not hereditary. However, if one member of a family has already been found to have an *APC* or *MYH* gene mutation, a negative result in any other family member means that person does not have FAP or its variants.

What if testing reveals that a person has inherited FAP or its variants?

Seventy-five percent of individuals with FAP will develop polyps by age 20, and nearly 90-percent will have polyps by age 30. Individuals with FAP have a 100 percent risk for developing colon cancer if they do not have their colon removed, with the average age of diagnosis between 35 and 43 years old. FAP patients have a 10 to12 percent lifetime risk for duodenal (part of the small intestine) cancer. Individuals with FAP are also at increased risk for thyroid, pancreatic and brain cancer, although the lifetime risk for each of these cancers is less than 2 percent. Children with FAP have a 1-2 percent risk for hepatoblastoma.

Although individuals with AFAP have fewer polyps, the lifetime risk for cancer remains high.

If a person has FAP or its variants, what are the options for cancer screening and prevention?

Patients with FAP should receive annual sigmoidoscopy or colonoscopy beginning at 10 years of age. Individuals with AFAP should have their first colonoscopy in their late teens and repeat it every one to two years. Discussion of prophylactic colectomy (removal of the colon before cancer develops) should begin in adolescence, since the colon is removed once there are too many adenomas to remove or follow. This surgery is usually done in the late teens or early 20s for patients with FAP but may be performed later or never for patients with AFAP. Depending on how much of the rectum (the part of the colon near the anus) is left after surgery, individuals with FAP may need to undergo a procedure called proctoscopy (scope of the rectum) every six to twelve months to check the rectum for polyps. It is estimated that up to half of FAP patients who retain the rectum after colectomy will require later surgical removal of the rectum because of uncontrolled polyps or rectal cancer. Therefore some physicians encourage removing the rectum along with the colon, especially for individuals with a significant number of rectal polyps. Individuals should be screened for polyps in the ileum (part of the small intestine) using a procedure called ileoscopy every three to five years after colectomy.

Individuals with FAP should also undergo a procedure called an upper endoscopy to screen for polyps in the stomach and duodenum. A baseline upper endoscopy with a side view should be done by age 25, and then repeated every one to five years depending on the number and size of polyps found.

To screen for thyroid cancers, a physical examination (palpation) and ultrasound have been suggested, especially for young women with FAP. Screening for hepatoblastoma (liver cancer) in children can include liver palpation, a serum alpha-fetoprotein blood test, and liver ultrasound each year up to age 6.

For families with a clinical diagnosis of FAP but without an identifiable gene mutation, or for individuals in these families who have not had genetic testing, at-risk family members should receive a sigmoidoscopy annually from ages 11-24, every two years from ages 25-34, every three years from ages 35-44, and then every three to five years after age 45. If polyps are found, screening should then follow the guidelines given above for individuals with FAP.

There is evidence that two medications, called Sulindac and Celebrex, may reduce the number of polyps in individuals with FAP. It is not yet clear whether they will also decrease the risk of developing cancer. Thus, Sulindac and Celebrex are used in addition to, but not in place of, the screening and surgical recommendations given above.

What are the possible risks and benefits of APC or MYH testing?

The only physical risks of testing are those of a routine blood draw. However, other risks and benefits should be considered before undergoing testing. The process of genetic testing may be emotionally difficult regardless of whether an *APC* or *MYH* mutation is found. Finding a gene mutation may indirectly provide information about other family members, who may have chosen not to be tested.

In addition, costs for the cancer screening and prevention options for a person with FAP may or may not be covered by their health insurance. Another issue with genetic testing is the possibility that the results could be used by an employer or insurance company to discriminate against a person. The Genetic Information Nondiscrimination Act (GINA) was signed into law in May 2008. GINA makes it illegal for health insurers to deny insurance coverage or charge a higher rate or premium to an otherwise healthy individual found to have a potential genetic condition or genetic predisposition towards a disease or disorder. Protections in health insurance went into effect in May 2009. GINA also makes it illegal for employers to use an employee's genetic information when making hiring, firing, placement, or promotion decisions. Employment protections took effect in November 2009. There are some groups for which GINA does not apply. If you have concerns about whether GINA applies to you, ask your genetic counselor. There is also a state law that offers protection.

What are the possible benefits of APC or MYH testing?

One of the major advantages of learning *APC* or *MYH* gene test results is reduced uncertainty about the risks of cancer and other FAP-related problems for people and their families. In addition, the testing may allow doctors to modify medical care to decrease the risk of cancer. Likewise, if *APC* or *MYH* testing is negative, it may allow doctors to decrease the frequency of cancer screening.

The decision to have *APC* or *MYH* testing is a complicated one. People and families must not only weigh the risks and benefits of testing, they must also consider their unique situations. Ultimately, people must make their own decisions.

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