Yale NewHaven Health
Smilow Cancer Hospital

Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

Hereditary Polyposis Syndromes

Smilow Cancer Genetics and Prevention Program

Colon ppolyps are growths in the colon that may become colorectal cancer if they are not removed. They are common in the general population and are usually not caused by an inherited or genetic risk. However, a small number of people who have multiple colon polyps have an inherited risk of developing polyps, known as a hereditary polyposis syndrome.

People with a hereditary polyposis syndrome usually develop more polyps over their lifetime, develop polyps earlier in life and may develop them more quickly compared with people in the general population. People who learn they have a hereditary polyposis syndrome are offered enhanced cancer screening and risk-reduction options. More information about hereditary polyposis syndromes follows.

Genetic testing is one way to determine if a person has a hereditary polyposis syndrome. If a person undergoes genetic testing, which finds a gene variant associated with a hereditary polyposis syndrome, it means the individual was born with an increased risk of developing polyps and certain types of cancers. The risk for colon polyps and cancer associated with pathogenic variants in these genes can vary. Genetic testing can look for several hereditary polyposis syndromes by testing multiple genes, including the *APC* and *MUTYH* genes, as well as additional genes related to hereditary polyposis syndromes. Some genes have not been studied as long as others, and some have only a *possible* association with risk of colon polyps and cancer. For these less-studied genes, information about the associated colon polyp and cancer risks, as well as screening recommendations, may change over time.

In addition, results of genetic testing provide important information to share with relatives because they may have also inherited the same increased risk of developing colon polyps and cancer. When a hereditary explanation is found in a family, relatives can have genetic testing to better understand their risk of developing cancer, which can help guide their decisions about cancer screening, prevention and management.

.

Familial adenomatous polyposis (FAP)

Familial adenomatous polyposis (FAP) is caused by a single pathogenic variant in the *APC* gene. People with "classic" FAP develop hundreds to thousands of adenomatous-type colon polyps, typically starting in their teens or twenties. If untreated, virtually all people with classic FAP will go on to develop colon cancer.

Additional findings associated with FAP include:

- Desmoid tumors (benign tumors, often in the abdominal region)
- Osteomas (bony tumors, particularly of the skull and jawbone)
- Congenital hypertrophy of the retinal pigment epithelium (CHRPE) (a benign eye finding)
- Tumors in the upper GI tract (stomach, small bowel and pancreas)
- Benign skin lesions (particularly epidermoid cyst)
- Cribriform-morular papillary thyroid cancer
- Medulloblastoma brain tumor

There is also "attenuated" FAP, which is a milder form of classic FAP. It is generally associated with fewer colon polyps and later age when colon polyps and cancer develop. People with attenuated FAP may not begin to develop polyps until 40 to 50 years of age. In general, people with attenuated FAP have more than 20 polyps, but often develop fewer than 100. Attenuated FAP is less commonly associated with the other additional FAP findings compared to those with classic FAP.

MUTYH-associated polyposis (MAP)

MUTYH-associated polyposis (MAP) is caused by **two** pathogenic variants in the *MUTYH* gene. People with MAP often have a milder form of polyposis. Generally, people with MAP develop fewer than 100 polyps over their lifetime and have later ages of onset of colon polyps (in their 40s–50s). Polyps are typically an adenomatous type; however, other types of polyps can also occur. If untreated, people with MAP have a lifetime risk of developing colorectal cancer ranging between 43 percent and 100 percent.

People with MAP also have an increased risk for small intestinal cancer and may develop stomach and small intestine polyps.

Juvenile polyposis syndrome

Juvenile polyposis syndrome (JPS) is caused by a single pathogenic variant in the *SMAD4* or *BMPR1A* gene. JPS causes multiple juvenile-type polyps in the colon, rectum, small intestine and stomach. These polyps are called "juvenile" because of their specific appearance under the microscope and not because of the age of the person when the polyp develops. Most people with JPS will develop polyps by the age of 20. The number of polyps that develop can vary from person to person with JPS. Some people may only have four to five polyps while others may have more than 100. If the polyps are not removed, they can cause problems, including intestinal blockage and cancer. The lifetime risk of colon cancer in people with JPS is up to 50 percent. The lifetime risk of stomach cancer is 15 – 21 percent and risk for gastrointestinal cancer is 46 –55 percent. The goal of close monitoring for polyps starting at a young age and the removal of any polyps that develop is to reduce the lifetime cancer risks associated with JPS.

Serrated polyposis syndrome

People with serrated polyposis syndrome (SPS) develop multiple serrated-type polyps throughout the colon. At this time, there is no single gene known to cause SPS. A diagnosis of this condition is based on a set of criteria rather than results of genetic testing.

SPS criteria, as defined by the World Health Organization include the presence of at least one of the following:

1) Five or more serrated-type polyps located in the colon, not to include the rectum, all being greater than 5 mm in size and with at least two polyps being greater than 10 mm in size; OR
2) More than 20 serrated polyps of any size distributed throughout the colon with greater than five polyps located in the colon, not to include the rectum.

A person with SPS has an increased risk of colorectal cancer. At this time, the exact lifetime risk for colorectal cancer is unknown. First-degree relatives of someone with SPS have an increased risk of colorectal cancer that is two to three times higher than the general population risk.

Other polyposis conditions

Clinical genetic testing has recently become available for several other genes that are associated with hereditary polyposis conditions, including *GREM1, MSH3, NTHL1, POLE, POLD1,* and others. Current data suggest people with pathogenic variants in these genes have an increased risk primarily for colon polyps and colon cancer. However, we are still learning about these genes and additional information will likely be available in the future.

There are also rarer hereditary cancer conditions, such as Peutz-Jeghers syndrome (due to a pathogenic variant in the *STK11* gene) and *PTEN* Hamartoma tumor syndrome (due to a pathogenic variant in the *PTEN* gene), that are associated with hamartomatous-type polyps.

Contact information

Smilow Cancer Genetics and Prevention Program
330 Orchard Street, Suite 107
New Haven, CT 06511
Phone: 203-200-4362
Fax: 203-200-1362
smilowcancergenetics@ynhh.org
http://yalecancercenter.org/patient/specialty/genetics/