SMAD4

The *SMAD4* 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 role of *SMAD4* is helping to regulate the stability and growth of cells in the gastrointestinal tract.

Like most genes, each person has two copies of the *SMAD4* gene, one inherited from each parent. A mutation in a single *SMAD4* gene inherited from either parent causes Juvenile Polyposis syndrome (JPS), which is associated with gastrointestinal polyps, especially a type of polyp called juvenile polyps, and is also known to increase the risks of certain cancers including colorectal, stomach, pancreatic, and small bowel.

Approximately 25% of individuals with JPS are the first in their family to carry the mutation.[1] 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.

Individuals with mutations in the *SMAD4* gene may also have a condition called Hereditary Hemorrhagic Telangiectasia (HHT).[2] HHT is associated with abnormal connections between blood vessels called arteries and veins (arteriovenous malformation, or AVM), which can occur in the lungs, brain, liver, and other parts of the body. One of the first symptoms of HHT is regular and frequent nosebleeds in childhood or later in life.

How common are mutations in the *SMAD4* gene?

Mutations in the *SMAD4* gene are rare—but approximately 20-25% of individuals with JPS have a pathogenic mutation in *SMAD4*.[3]

How mutations in this gene impact risk

Women

If a woman has a mutation in the *SMAD4* gene, her chances of developing colorectal, stomach, pancreatic, and small bowel cancer 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.

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[1] Larsen Haidle J, Howe JR. 2015 December 3. Juvenile Polyposis Syndrome. In: GeneReviews® (database online). Copyright, University of Washington, Seattle. 1993-2016. Available at http://www.ncbi.nlm.nih.gov/books/NBK1469/. April 21, 2016.
[2] Aretz S, Stienen D, Uhlhaas S, et al. High proportion of large genomic deletions and a genotype phenotype update in 80 unrelated families with juvenile polyposis syndrome. J Med Genet. 2007;44(11):702-9.
[3] Howe JR, Mitros FA, Summers RW. The risk of gastrointestinal carcinoma in familial juvenile polyposis. Ann Surg Oncol. 1998;5(8):751-6.

Cancer by age 80	Average US woman[4]	With *SMAD4* mutation
Colorectal	2.8%	39%[5,6]
Stomach	<1%	Elevated (21%)[5]
Pancreatic	<1%	Elevated[5]
Small Bowel (Duodenal)	<1%	Elevated[5]

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

Men

If a man has a mutation in the *SMAD4* gene, his chances of developing colorectal, stomach, pancreatic, and small bowel cancer 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.

Cancer by age 80	Average US man[4]	With *SMAD4* mutation
Colorectal	3.4%	39%[5, 6]
Stomach	<1%	Elevated (21%)[5]
Pancreatic	1.1%	Elevated[5]
Small Bowel (Duodenal)	<1%	Elevated[5]

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

Screening guidelines

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).[7] They are for individuals with JPS who have a mutation in the *SMAD4* 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.

[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] Howe JR, Mitros FA, Summers RW. The risk of gastrointestinal carcinoma in familial juvenile polyposis. Ann Surg Oncol. 1998;5(8):751-6.
[6] Brosens LA, Van hattem A, Hylind LM, et al. Risk of colorectal cancer in juvenile polyposis. Gut. 2007;56(7):965-7.
[7] 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[8]

- **Starting around age 15:** Colonoscopy every 2-3 years, or every year if polyps are found.

Stomach cancer[8]

- **Starting around age 15:** Upper endoscopy every 2-3 years, or every year if polyps are found. If multiple polyps lead to anemia requiring blood transfusion, your provider may discuss surgical removal of the stomach (gastrectomy).

Pancreatic cancer

- Currently, there are no pancreatic cancer screening guidelines from the NCCN specific to *SMAD4* mutation carriers. Your provider may discuss screening or referral to a specialist.

Small bowel cancer (duodenal and other sections)

- Currently, there are no small bowel cancer screening guidelines from the NCCN specific to *SMAD4* mutation carriers. Your provider may discuss screening or referral to a specialist.

Other *SMAD4*-related recommendations

- Speak with your provider about screening recommended for individuals who may have HHT.

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