Genetic Insights: quick reference guide for healthcare providers

This guide is intended to facilitate a discussion between a provider and their patient.

Genetic Insights test results: **Juvenile polyposis syndrome/hereditary hemorrhagic telangiectasia (*SMAD4*-associated)**

Key results

A pathogenic or likely pathogenic variant associated with juvenile polyposis syndrome (JPS) was found in the *SMAD4* gene.

People with JPS have a significantly increased risk of developing gastrointestinal polyps, colon cancer, and certain other cancers. People with a DNA variant in *SMAD4* may also have features of hereditary hemorrhagic telangiectasia (HHT).

Next steps

Clinical recommendations	Resources
Genetic Insights is a screening test and not intended for diagnosis. A follow-up genetic test should be performed in a clinical setting before any other action is taken.	**Ready to order?** Check with your institution and/or patient's insurance about the preferred testing laboratory. Blueprint Genetics® offers hereditary cancer testing. To confirm this test result, **targeted variant testing** for the variant identified is available. You can order a confirmation test here: Blueprint Genetics/TVT **Have questions?** Call **1.866.GENE.INFO** (1.866.436.3463) to speak to a specialized Quest genetic counselor or geneticist available to healthcare providers to discuss test selection and results.
Refer your patient to a genetic counselor specializing in hereditary cancer. *Genetic counselors can provide counseling on the implications of this test result and next steps for your patient.*	Your patient can schedule a 1-on-1 remote genetic counseling session through their online Genetic Insights Cancer Risk Report at no additional cost. To find a genetic counselor with expertise in hereditary cancer genetics practicing in your patient's area for an in-person session, please visit FindAGeneticCounselor.NSGC.org

Patient conversation starters:

Patient conversation starters summarize the preceding information in plain language to support meaningful conversations between you and your patient.

FindAGeneticCounselor.NSGC.org

Your Genetic Insights test is a screening test. The next step is to have your result confirmed with a second genetic test.

It's also important that you talk with a genetic counselor. Genetic counselors are experts in genetics and can help you understand this result and potential next steps.

You can access a genetic counselor through your online Genetic Insights dashboard at no additional cost to you, and we can discuss a referral to a local genetic counselor.

Visit QuestDiagnostics.com/Genetic-Health-Screening for more information about this test.

What is JPS/HHT?

JPS is a hereditary cancer predisposition syndrome characterized by the presence of juvenile hamartomatous polyps in the gastrointestinal tract and a higher lifetime risk of colon and certain other cancers, typically with an earlier age of onset.[1,2]

Polyps may develop between infancy and adulthood. The mean age of colon cancer diagnosis is 42 years.[1]

Polyps can appear in the stomach, small intestine, colon, and rectum and, if untreated, may lead to complications such as obstruction and bleeding. Most juvenile polyps are benign.[1]

Clinical diagnosis of JPS may be made based on standardized clinical criteria. JPS is associated with DNA variants in the *BMPR1A* and *SMAD4* genes, although in about 45% of those with a clinical diagnosis, a genetic cause cannot be identified.[1]

People with JPS due to a *SMAD4* variant may also have features of hereditary hemorrhagic telangiectasia (HHT), a genetic condition characterized by arteriovenous malformations (AVMs). Clinical signs of HHT can emerge in early childhood and may include nose bleeds, telangiectasias, as well as AVMs.

Management is best coordinated by a specialized care team.[1,2] Individuals with JPS are recommended to undergo more frequent cancer screening, typically starting at 12-15 years old.[2]

See the Management options section for more detail.

Patient conversation starters:

Juvenile polyposis syndrome and hereditary hemorrhagic telangiectasia (JPS/HHT) are caused by DNA variants in certain genes.

People with JPS/HHT have a higher than typical chance of developing colon cancer. But not everyone with JPS/HHT will develop colon cancer.

People with JPS/HHT can also develop a certain type of polyps in their stomach and gastrointestinal tract. The polyps aren't cancerous but can cause certain health problems. People with a DNA variant in *SMAD4* can also have signs of HHT. HHT can cause bleeding, like having a nosebleed for no reason.

People with HHT should have cancer screenings earlier in life and more often than typical. This increases the chance that if cancer develops, it's detected as early as possible.

What this result means for family members

There are 2 primary ways someone can have a DNA variant linked to JPS/HHT:

- The DNA variant can be inherited from a biological parent. In this case, at least 1 parent has the same DNA variant. Each full sibling and each child of someone with the variant has a 50% chance of having it as well
- The DNA variant can arise in someone for the first time (called a de novo variant). In this case, their children have a 50% chance of having the variant as well. Neither biological parent nor any siblings are likely to have the variant

In people with a confirmed DNA variant associated with JPS/HHT, genetic testing for family members may help inform their risks and screening protocols.[3]

A genetic counselor can help determine the most appropriate testing options. Therefore, it is strongly recommended that people share their results with their biological relatives.

Patient conversation starters:

There are 2 ways someone can end up having a DNA variant linked to JPS/HHT.

First, it can be passed down from a parent. In this case, 1 parent would have that same DNA variant. Full siblings would have a 50% chance (1 in 2 chance) of having the DNA variant too.

Second, it is possible that the DNA variant happens in someone in a family for the first time. In this case, your parents and siblings are not likely to have this variant.

However, in either case, each child of someone with a DNA variant linked to JPS/HHT has a 50% chance of having the same DNA variant.

Sharing this result with your family members is important so they can talk to a healthcare provider about genetic testing.

Cancer risk

Select estimated cancer risks in people with JPS compared to the general population include[2]:

Cancer type	Approximate lifetime risk with JPS	Approximate lifetime risk in the general population
Colon	Up to 50%	4.5%
Stomach	Up to 21%	<1%
Small intestine	Undefined, risk may be increased	<1%

See NCCN Guidelines® for full description of associated cancers and risks. Associated cancers and risks may change over time as medical research advances.

Management options

There are options for cancer prevention and early detection for people with a DNA variant in *SMAD4*. Clinical guidelines from the National Comprehensive Cancer Network® (NCCN®) in adults with a *SMAD4* DNA variant and no personal history of an associated cancer include[2]:

Condition	Guidelines for people with confirmed JPS and *SMAD4* variant
Colon cancer *Stomach cancer*	Colonoscopy and upper endoscopy beginning at ~18 years of age Repeat every 1-3 years Consider surgical evaluation if polyp burden becomes too high
Small intestine cancer	No screening recommendations have been made at this time
HHT	Screen for signs, symptoms, and vascular lesions associated with HHT

Patient conversation starters:

It's recommended that people with JPS/HHT have cancer screenings earlier and more often than typical. This way, cancer is more likely to be caught in the early stages when it's most treatable.

If your result is confirmed, it's important to work with the right specialists, like a medical oncologist and a geneticist, to find cancer screening and risk-reducing options that are right for you.

See NCCN for complete recommendations including recommendations during childhood.[2] Recommendations may change over time.
If the test result is confirmed, local centers for excellence in hereditary cancer should be consulted for further clinical management.

Additional resources

The following advocacy groups have additional information and resources about risk for hereditary colon cancer and HHT:

Colorectal Cancer Alliance: CCAlliance.org
Cure HHT: CureHHT.org
Facing Our Risk of Cancer Empowered (FORCE): FacingOurRisk.org
Fight Colorectal Cancer: FightColorectalCancer.org

References

1. Larsen HJ, MacFarland SP, Howe JR. Juvenile Polyposis Syndrome. May 13, 2003. Updated February 3, 2022. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews® [Internet]. University of Washington, Seattle; 1993-2022. https://www.ncbi.nlm.nih.gov/books/NBK1469/
2. National Comprehensive Cancer Network®. Genetic/Familial High-Risk Assessment: Colorectal (Version 2.2022). NCCN Guidelines®. Accessed December 13, 2022. www.nccn.org

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