SMAD4 gene

Associated Syndrome Name: Juvenile polyposis syndrome (JPS) and hereditary hemorrhagic telangiectasia (HHT)

SMAD4 Summary Cancer Risk Table

CANCER	GENETIC CANCER RISK
Colorectal	High Risk
Gastric	High Risk
Other	High Risk
Other	Elevated Risk

SMAD4 gene Overview

Juvenile polyposis syndrome (JPS) and hereditary hemorrhagic telangiectasia (HHT) [1, 2, 3, 4, 5]

- Individuals with *SMAD4* mutations have both juvenile polyposis syndrome (JPS) and hereditary hemorrhagic telangiectasia (HHT).
- Patients with JPS have a high risk for cancer as a result of hamartomatous polyps in the gastrointestinal system, particularly in the colon, rectum and stomach. The presence of these polyps is associated with a high risk for colorectal cancer, and can cause bleeding leading to anemia.
- Patients with JPS also have an elevated risk for small bowel cancer.
- This patient also has hereditary hemorrhagic telangiectasia (HHT), which is associated with a high risk for life-threatening arteriovenous malformations of the lungs, brain and liver, as well as nosebleeds.
- Recent studies suggest that patients with *SMAD4* mutations have an increased risk for connective tissue disorders such as thoracic aortic disease, brain aneurysm, and lax skin and joints. The data for this are not yet conclusive and there are currently no medical management recommendations associated with connective tissue disorders for carriers of *SMAD4* mutations.
- Although there are high risks for cancer in patients with JPS, and high risks for life-threatening complications from the arteriovenous malformations found in patients with HHT, these risks can be greatly reduced with appropriate medical management. Guidelines from the National Comprehensive Cancer Network (NCCN) and the Scientific Advisory Committee of the HHT Foundation are listed below. It is recommended that patients with *SMAD4* mutations and diagnoses of JPS and HHT be managed by a multidisciplinary team with experience in the prevention and treatment of the complications associated with these conditions.

SMAD4 gene Cancer Risk Table

CANCER TYPE	AGE RANGE	CANCER RISK	RISK FOR GENERAL POPULATION
Colorectal	To age 42 [2, 6]	20%-25%	<0.2%
	To age 80 [2, 5, 6]	40%-50%	2.8%
Gastric	To age 80 [5, 6]	Up to 21%	0.6%
Small Bowel	To age 80 [2, 5, 6]	Rare, but elevated risk	0.2%
Other - hereditary hemorrhagic telangiectasia (HHT)	All ages [1]	HHT is associated with a high risk for life threatening arteriovenous malformations of the lungs, brain and liver as well as nosebleeds.	NA

SMAD4 Cancer Risk Management Table

The overview of medical management options provided is a summary of professional society guidelines. The most recent version of each guideline should be consulted for more detailed and up-to-date information before developing a treatment plan for a particular patient.

This overview is provided for informational purposes only and does not constitute a recommendation. While the medical society guidelines summarized herein provide important and useful information, medical management decisions for any particular patient should be made in consultation between that patient and his or her healthcare provider and may differ from society guidelines based on a complete understanding of the patient's personal medical history, surgeries and other treatments.

CANCER TYPE	PROCEDURE	AGE TO BEGIN	FREQUENCY (UNLESS OTHERWISE INDICATED BY FINDINGS)
Colorectal	Colonoscopy[5, 7, 8]	12 to 15 years, or earlier if symptoms are present	Every 1 to 3 years, depending on age and findings
	Monitor for rectal bleeding and/or anemia.[3, 7, 8]	15 years, or earlier if symptoms are present	Annually
Gastric	Upper endoscopy[5, 7]	12 to 15 years	Every 1 to 3 years, depending on age and findings
Small Bowel	Currently there are no specific medical management guidelines for small bowel cancer risk in mutation carriers.	NA	NA
Other - hereditary hemorrhagic telangiectasia (HHT)	Multiple screenings recommended, which may include brain MRI, contrast echocardiogram, and chest CT.[1]	Some screenings are recommended within the first 6 months of life or at time of diagnosis	Varies

Information for Family Members

The following information for Family Members will appear as part of the MMT for a patient found to have a mutation in the SMAD4 gene.

This patient's relatives are at risk for carrying the same mutation(s) and associated cancer risks as this patient. Cancer risks for females and males who have this/these mutation(s) are provided below.

Family members should talk to a healthcare provider about genetic testing. Close relatives such as parents, children, brothers and sisters have the highest chance of having the same mutation(s) as this patient. Other more distant relatives such as cousins, aunts, uncles, and grandparents also have a chance of carrying the same mutation(s). Testing of at-risk relatives can identify those family members with the same mutation(s) who may benefit from surveillance and early intervention.

Since *SMAD4* mutations carry a risk for complications in children and some screenings are recommended to begin in infancy, mutation testing should occur shortly after birth.[5]

References

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7. Boland CR, et al. Diagnosis and Management of Cancer Risk in the Gastrointestinal Hamartomatous Polyposis Syndromes: Recommendations From the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2022 162(7):2063-2085. PMID: 35487791.

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