Test Definition: SMADZ

SMAD4 Gene, Full Gene Analysis

Overview

Useful For

Confirmation of juvenile polyposis syndrome or juvenile polyposis/hereditary hemorrhagic telangiectasia for patients with clinical features

This test should be ordered only for individuals with symptoms suggestive of juvenile polyposis syndrome or juvenile polyposis/hereditary hemorrhagic telangiectasia. Asymptomatic patients with a family history of juvenile polyposis syndrome or juvenile polyposis/hereditary hemorrhagic telangiectasia should not be tested until a mutation has been identified in an affected family member.

Additional Tests

Test ID	Reporting Name	Available Separately	Always Performed
COLAB	Hereditary Colon Cancer CGH Array	Yes, (order FMTT)	Yes

Testing Algorithm

When this test is ordered, comparative genomic hybridization array will always be performed at an additional charge.

See Colonic Polyposis Syndromes Testing Algorithm in Special Instructions.

Special Instructions

- Molecular Genetics: Inherited Cancer Syndromes Patient Information
- Informed Consent for Genetic Testing
- Colonic Polyposis Syndromes Testing Algorithm
- Informed Consent for Genetic Testing (Spanish)

Method Name

Polymerase Chain Reaction (PCR) Amplification/DNA Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Shipping Instructions

Specimen preferred to arrive within 96 hours of draw.

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Specimen Type: Whole blood

Container/Tube:

Preferred: Lavender top (EDTA) or yellow top (ACD)

Acceptable: Any anticoagulant

Specimen Volume: 3 mL

Collection Instructions:

1. Invert several times to mix blood.

2. Send specimen in original tube.

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing-Spanish (T826)

2. Molecular Genetics: Inherited Cancer Syndromes Patient Information (T519) in Special Instructions

Specimen Minimum Volume

1 mL

Reject Due To

All specimens will be evaluated by Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Ambient (preferred)		
	Frozen		
	Refrigerated		

Clinical and Interpretive

Clinical Information

Juvenile polyposis syndrome (JPS) is a rare hereditary cancer predisposition syndrome caused by mutations in the *SMAD4* or *BMPR1A* genes. JPS is characterized by the presence of multiple histologically defined juvenile polyps in the upper and/or lower gastrointestinal (GI) tract and an increased risk for GI cancers. Age of onset for cancer development is typically in the second or third decade of life, although some patients present with a more severe infantile-onset form of the disease. JPS is inherited in an autosomal dominant fashion, although a significant proportion of probands have no family history. Approximately 50% of patients with JPS have an identifiable mutation in the *SMAD4* or *BMPR1A* genes.

Of note, some patients with mutations in the *SMAD4* gene exhibit a combined juvenile polyposis/hereditary hemorrhagic telangiectasia phenotype (JP/HHT). Clinical features of HHT include development of arteriovenous malformations (AVMs) of the skin, mucosa, and viscera; spontaneous, recurrent epistaxis (nosebleeds); as well as additional complications such as transient ischemic attacks, embolic stroke, heart failure, cerebral abscess, massive hemoptysis, massive hemothorax, seizure, and cerebral hemorrhage.

Reference Values

An interpretive report will be provided.

Interpretation

All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity, and reported with interpretive comments detailing their potential or known significance.

Cautions

A small percentage of individuals who are carriers or have a diagnosis of juvenile polyposis syndrome or juvenile polyposis/hereditary hemorrhagic telangiectasia may have a mutation that is not identified by this method (eg, promoter mutations). The absence of a mutation, therefore, does not eliminate the possibility of positive carrier status or the diagnosis of juvenile polyposis syndrome or juvenile polyposis/hereditary hemorrhagic telangiectasia. For carrier testing, it is important to first document the presence of a *SMAD4* gene mutation in an affected family member.

We strongly recommend that patients undergoing predictive testing receive genetic counseling both prior to testing and after results are available.

In some cases, DNA alterations of undetermined significance may be identified.

Rare polymorphisms exist that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings, additional testing should be considered.

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Errors in our interpretation of results may occur if information given is inaccurate or incomplete.

Clinical Reference

1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015 May;17(5):405-424

2. Brosens LAA, Langeveld D, van Hattern WA, et al: Juvenile Polyposis syndrome. World J Gastroenterol 2011;17(44):4839-4844

3. Calva-Cerqueira D, Chinnathambi S, Bechman B, et al: The rate of germline mutations and large deletions of SMAD4 and BMPR1A in juvenile polyposis. Clin Genet 2009;75:79-85

4. Brosens LAA, van Hattern A, Hylind LM, et al: Risk of colorectal cancer in juvenile polyposis. Gut 2007;56:965-967

5. Gallione C, Aylsworth A, Beis J, et al: Overlapping spectra of SMAD4 mutations in Juvenile Polyposis (JP) and JP-HHT syndrome. Am J of Med Genet Part A 2010;152:333-339

6. Larsen Haidle J, Howe JR: Juvenile Polyposis Syndrome. In GeneReviews. University of Washington, Seattle, 1993-2014. 2003 May 13. Edited by RA Pagon, MP Adam, HH Ardinger, et al. Available at www.ncbi.nlm.nih.gov/books/NBK1469

Performance

Method Description

Bidirectional sequence analysis is performed to test for the presence of a mutation in all coding regions and intron/exon boundaries of the *SMAD4* gene.(Unpublished Mayo method)

Additionally, array comparative genomic hybridization (aCGH) is used to test for the presence of large deletions and duplications.(Aradhya S, Lewis R, Bonaga T, et al: Exon-level array CGH in a large clinical cohort demonstrates increased sensitivity of diagnostic testing for Mendelian disorders. Genet Med 2012;14[6]:594-603)

PDF Report

No

Day(s) and Time(s) Test Performed

Performed weekly, Varies

Analytic Time

14 days

Maximum Laboratory Time

20 days

Specimen Retention Time

Whole Blood: 2 weeks (if available) Extracted DNA: 3 months

Performing Laboratory Location

Rochester

Fees and Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information

81406 SMAD4 (SMAD family member 4) (eg, hemorrhagic telangiectasia syndrome, juvenile polyposis), full gene sequence

Hereditary Colon Cancer CGH Array

81228-Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, Bacterial Artificial Chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
SMADZ	SMAD4 Gene, Full Gene Analysis	77624-5

Result ID	Test Result Name	Result LOINC Value
52528	Result Summary	50397-9
52529	Result	82939-0
52530	Interpretation	69047-9
52531	Additional Information	48767-8
52532	Specimen	31208-2
52533	Source	31208-2
52534	Array Billed?	No LOINC Needed
52535	Released By	18771-6