

Overview

Useful For

Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of Noonan syndrome (NS) or related disorders

Establishing a diagnosis of a NS or related disorders, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved

Identifying variants within genes known to be associated with increased risk for disease features allowing for predictive testing of at-risk family members

Genetics Test Information

This test uses next-generation sequencing to test for variants in the *BRAF*, *CBL*, *HRAS*, *KRAS*, *MAP2K1*, *MAP2K2*, *NRAS*, *PTPN11*, *RAF1*, *SHOC2*, and *SOS1* genes.

This test may aid in the diagnosis of Noonan syndrome, LEOPARD syndrome, cardiofaciocutaneous syndrome, Costello syndrome, or a related disorder. This test cannot distinguish between germline variants associated with Noonan syndrome and related disorders versus somatic (oncogenic, nongermline) variants, which may be associated with hematologic neoplasms. Therefore, this test does not provide diagnostic, prognostic, or therapeutic information for somatic variants. Variants detected by this test are interpreted as germline unless otherwise noted in the interpretation.

Identification of a pathogenic variant may assist with prognosis, clinical management, familial screening, and genetic counseling.

[Prior Authorization](#) is available for this assay.

Special Instructions

- [Informed Consent for Genetic Testing](#)
- [Noonan Spectrum Gene Testing Patient Information Sheet](#)
- [Noonan Syndrome and Related Disorders Multi-Gene Panel Prior Authorization Ordering Instructions](#)
- [Informed Consent for Genetic Testing \(Spanish\)](#)

Highlights

This test includes next-generation sequencing and supplemental Sanger sequencing to evaluate the genes tested on this

panel.

Method Name

Custom Sequence Capture and Targeted Next-Generation Sequencing followed by Polymerase Chain Reaction (PCR) and Supplemental Sanger Sequencing

NY State Available

Yes

Specimen

Specimen Type

Whole Blood EDTA

Ordering Guidance

This test has been validated for testing prenatal specimens. Contact a laboratory genetic counselor at 800-533-1710 for specimen collection requirements or questions related to prenatal testing for Noonan syndrome and related disorders.

Targeted testing for familial variants (also called site-specific or known mutation testing) is available for the genes on this panel. See FMTT / Familial Mutation, Targeted Testing, Varies.

Necessary Information

- [Noonan Spectrum Gene Testing Patient Information Sheet](#) (T689) is strongly recommended, but not required, to be filled out and sent with the specimen. This information aids in providing a more thorough interpretation of test results. Ordering providers are strongly encouraged to complete the form and send it with the specimen.
- Include physician name and phone number with specimen.
- [Prior Authorization](#) is available for this assay. **Submit the required form with the specimen.**

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.

Container/Tube: Lavender top (EDTA)

Specimen Volume: 3 mL

Collection Instructions: Send specimen in original tube. **Do not** aliquot.

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:

[-Informed Consent for Genetic Testing \(T576\)](#)

[-Informed Consent for Genetic Testing-Spanish \(T826\)](#)

2. [Noonan Spectrum Gene Testing Patient Information Sheet \(T689\)](#)

3. [Noonan Syndrome and Related Disorders Multi-Gene Panel Prior Authorization Ordering Instructions](#)

4. If not ordering electronically, complete, print, and send a [Cardiovascular Test Request \(T724\)](#) with the specimen.

Reject Due To

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

Specimen Minimum Volume

1 mL

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Whole Blood EDTA	Ambient (preferred)		
	Refrigerated		

Clinical & Interpretive

Clinical Information

Noonan syndrome (NS) is an autosomal dominant disorder of variable expressivity characterized by short stature, congenital heart defects, characteristic facial dysmorphism, unusual chest shape, developmental delay of varying degree, cryptorchidism, and coagulation defects, among other features.

Heart defects include pulmonary valve stenosis (20%-50%), hypertrophic cardiomyopathy (20%-30%), atrial septal defects (6%-10%), ventricular septal defects (approximately 5%), and patent ductus arteriosus (approximately 3%). Facial features, which tend to change with age, may include hypertelorism, downward-slanting eyes, epicanthal folds, and low-set and posteriorly rotated ears. Mild intellectual disability is seen in up to one-third of adults.

The incidence of NS is estimated to be between 1 in 1000 and 1 in 2500, although subtle expression in adulthood may

cause this number to be an underestimate. NS is genetically heterogeneous, with 4 genes currently associated with the majority of cases: PTPN11, RAF1, SOS1, and KRAS. Heterozygous variants in NRAS, HRAS, BRAF, SHOC2, MAP2K1, MAP2K2, and CBL have also been associated with a smaller percentage of NS and related phenotypes. All of these genes are involved in a common signal transduction pathway known as the Ras-mitogen-activated protein kinase (MAPK) pathway. The MAPK pathway is important for cell growth, differentiation, senescence, and death. Molecular genetic testing of all of the known genes identifies a variant in approximately 75% of affected individuals. NS can be sporadic and due to new variants; however, an affected parent can be recognized in 30% to 75% of families.

Some studies have shown that there is a genotype-phenotype correlation associated with NS. An analysis of a large cohort of individuals with NS has suggested that PTPN11 variants are more likely to be found when pulmonary stenosis is present, while hypertrophic cardiomyopathy is commonly associated with RAF1 variants, but rarely associated with PTPN11.

A number of related disorders exist that have phenotypic overlap with NS and are caused by variants in the same group of genes. PTPN11 and RAF1 variants have been associated with LEOPARD (lentiginos, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and deafness) syndrome, an autosomal dominant disorder sharing several clinical features with NS. Variants in BRAF, MAP2K1, MAP2K2, and KRAS have been identified in individuals with cardiofaciocutaneous (CFC) syndrome, a condition involving congenital heart defects, cutaneous abnormalities, Noonan-like facial features, and severe psychomotor developmental delay. Costello syndrome, which is characterized by coarse facies, short stature, distinctive hand posture and appearance, severe feeding difficulty, failure to thrive, cardiac anomalies, and developmental disability has been primarily associated with variants in HRAS. Variation in SHOC2 has been associated with a distinctive phenotype involving features of NS and loose anagen hair.

Genes included in the Noonan Syndrome and Related Disorders Multi-Gene Panel

Gene	Protein	Inheritance	Disease association
<i>BRAF</i>	V-RAF murine sarcoma viral oncogene homolog b1	AD	Noonan/CFC/Costello syndrome
<i>CBL</i>	CAS-BR-M murine ecotropic retroviral transforming sequence homolog	AD	Noonan syndrome-like disorder
<i>HRAS</i>	V-HA-RAS Harvey rat sarcoma viral oncogene homolog	AD	Costello syndrome
<i>KRAS</i>	V-KI-RAS Kirsten rat sarcoma viral oncogene homolog	AD	Noonan/CFC/Costello syndrome
<i>MAP2K1</i>	Mitogen-activated protein kinase kinase 1	AD	Noonan/CFC
<i>MAP2K2</i>	Mitogen-activated protein kinase	AD	Noonan/CFC

	kinase 2		
<i>NRAS</i>	Neuroblastoma ras viral oncogene homolog	AD	Noonan syndrome
<i>PTPN11</i>	Protein-tyrosine phosphatase, nonreceptor-type, 11	AD	Noonan/CFC/LEOPARD syndrome
<i>RAF1</i>	V-raf-1 murine leukemia viral oncogene homolog 1	AD	Noonan/LEOPARD syndrome
<i>SHOC2</i>	Suppressor of clear, c. Elegans, homolog of	AD	Noonan-syndrome like with loose anagen hair
<i>SOS1</i>	Son of sevenless, drosophila, homolog 1	AD	Noonan-syndrome like with loose anagen hair

Abbreviations: Autosomal dominant (AD)

Reference Values

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

Interpretation

Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Cautions

Clinical Correlations:

Some individuals who have involvement of 1 or more of the genes on the panel may have a variant that is not identified by the methods performed (eg, promoter variants, deep intronic variants). The absence of a variant, therefore, does not eliminate the possibility of Noonan syndrome (NS) or a related disorder.

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

If testing was performed because of a family history of NS or a related disorder, it is often useful to first test an affected family member. Identification of a pathogenic variant in an affected individual would allow for more informative testing of at-risk individuals.

If clinical or family history suggests that a detected variant may be somatic and not germline, additional genetic testing of alternate tissue types or appropriate counseling and medical management may be indicated. In addition, a negative result does not preclude the presence of a somatic variant at low (<10%) variant allele frequency.

Technical Limitations:

Next-generation sequencing may not detect all types of genetic variants. Additionally, rare alterations (ie, polymorphisms) may be present that could lead to false-negative or false-positive results. If results do not match clinical findings, consider alternative methods for analyzing these genes, such as Sanger sequencing or large deletion/duplication analysis.

If the patient has had an allogeneic blood or marrow transplant or a recent (ie, less than 6 weeks from time of sample collection) heterologous blood transfusion these results may be inaccurate due to the presence of donor DNA.

Reclassification of Variants Policy:

At this time, it is not standard practice for the laboratory to systematically review likely pathogenic variants or variants of uncertain significance that are detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time.

Contact the laboratory if additional information is required regarding the transcript or human genome assembly used for the analysis of this patient's results.

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. Tartaglia M, Gelb BD, Zenker M: Noonan syndrome and clinically related disorders. *Best Pract Res Clin Endocrinol Metab.* 2011 Feb;25(1):161-179
3. Rauen KA: Cardiofaciocutaneous syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews* [Internet].

University of Washington, Seattle; 2007. Updated March 3, 2016. Accessed August 2, 2021. Available at www.ncbi.nlm.nih.gov/books/NBK1186/

4. Allanson JE, Roberts AE: Noonan syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington. Seattle; 2001. Updated August 8, 2019. Accessed August 2, 2021. Available at www.ncbi.nlm.nih.gov/books/NBK1124/

5. Gripp KW, Rauen KA: Costello syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2006. Updated August 29, 2019. Accessed August 2, 2021. Available at www.ncbi.nlm.nih.gov/books/NBK1507/

6. Gelb BD, Tartaglia M: Noonan syndrome with multiple lentigines. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 2007. Updated May 14, 2015. Accessed August 2, 2021. Available at www.ncbi.nlm.nih.gov/books/NBK1383/

Performance

Method Description

Next-generation sequencing (NGS) is performed using an Illumina instrument with paired-end reads. The DNA is prepared for NGS using a custom Agilent SureSelect Target Enrichment System. Data is analyzed with a bioinformatics software pipeline. Supplemental and/or confirmatory Sanger sequencing is performed when necessary. (Unpublished Mayo method)

Genes analyzed: *BRAF*, *CBL*, *HRAS*, *KRAS*, *MAP2K1*, *MAP2K2*, *NRAS*, *PTPN11*, *RAF1*, *SHOC2*, and *SOS1*.

PDF Report

No

Specimen Retention Time

Extracted DNA: 2 months

Performing Laboratory Location

Rochester

Fees & Codes

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 US Food and Drug Administration.

CPT Code Information

81479-CBL

81404-HRAS

81311-NRAS

81405 x 2-KRAS, SHOC2

81406 x 6-BRAF, MAP2K1, MAP2K2, PTPN11, RAF1, SOS1

Prior Authorization

Insurance preauthorization is available for this testing; forms are available.

Patient financial assistance may be available to those who qualify. Patients who receive a bill from Mayo Clinic Laboratories will receive information on eligibility and how to apply.

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
NSRGP	Noonan Syndrome and Related Panel,B	In Process

Result ID	Reporting Name	LOINC®
36821	Gene(s) Evaluated	48018-6
36822	Result Summary	50397-9
36823	Result Details	82939-0
36824	Interpretation	59462-2
36953	Additional Information	48767-8
36954	Method	85069-3
36955	Disclaimer	62364-5
36825	Reviewed by	18771-6