

## Overview

### Useful For

Providing a genetic evaluation for patients with a personal or family history suggestive of Noonan syndrome, Noonan syndrome with multiple lentigines, Noonan syndrome with loose anagen hair, cardiofaciocutaneous syndrome, Costello syndrome, Baraitser-Winter syndrome, Legius syndrome, and related conditions

Establishing a diagnosis of Noonan syndrome, Noonan syndrome with multiple lentigines, Noonan syndrome with loose anagen hair, cardiofaciocutaneous syndrome, Costello syndrome, Baraitser-Winter syndrome, Legius syndrome, and related conditions

### Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
_STR1	Comp Analysis using STR (Bill only)	No, (Bill only)	No
_STR2	Add'l comp analysis w/STR (Bill Only)	No, (Bill only)	No
CULFB	Fibroblast Culture for Genetic Test	Yes	No
CULAF	Amniotic Fluid Culture/Genetic Test	Yes	No
MATCC	Maternal Cell Contamination, B	Yes	No

### Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in 20 genes associated with Noonan syndrome and related conditions: *ACTB*, *ACTG1*, *BRAF*, *CBL*, *HRAS*, *KRAS*, *LZTR1*, *MAP2K1*, *MAP2K2*, *MRAS*, *NRAS*, *PPP1CB*, *PTPN11*, *RAF1*, *RIT1*, *RRAS2*, *SHOC2*, *SOS1*, *SOS2*, and *SPRED1*. See [Targeted Genes and Methodology Details for Noonan Syndrome and Related Conditions Gene Panel](#) and Method Description for additional details.

This test may aid in the diagnosis of Noonan syndrome, Noonan syndrome with multiple lentigines, cardiofaciocutaneous syndrome, Costello syndrome, or a related disorder. This test is not intended or validated for detection of somatic variants and 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. If a patient has active hematological malignancy, skin biopsy is recommended (instead of whole blood) for detection of germline variants.

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Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, familial screening, and genetic counseling for Noonan syndrome, Noonan syndrome with multiple lentigines, Noonan syndrome with loose anagen hair, cardiofaciocutaneous syndrome, Costello syndrome, Baraitser-Winter syndrome, Legius syndrome, and related conditions.

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

### Testing Algorithm

#### For prenatal specimens only:

-If amniotic fluid (nonconfluent cultured cells) is received, amniotic fluid culture/genetic test will be added at an additional charge.

-If chorionic villus specimen (nonconfluent cultured cells) is received, fibroblast culture for genetic test will be added at an additional charge.

For any prenatal specimen that is received, maternal cell contamination testing will be performed at an additional charge.

### Special Instructions

- [Informed Consent for Genetic Testing](#)
- [Noonan Spectrum Gene Testing Patient Information Sheet](#)
- [Informed Consent for Genetic Testing \(Spanish\)](#)
- [Targeted Genes and Methodology Details for Noonan Syndrome and Related Conditions Gene Panel](#)
- [Noonan Syndrome and Related Panel \(NSRGG\) Prior Authorization Ordering Instructions](#)

### Method Name

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

### NY State Available

Yes

## Specimen

### Specimen Type

Varies

### Ordering Guidance

Customization of this panel and single gene analysis for any gene present on this panel are available. For more information see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies.

Targeted testing for familial variants (also called site-specific or known mutations testing) is available for the genes on this panel. See FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.

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**Additional Testing Requirements**

All prenatal specimens must be accompanied by a maternal blood specimen; order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen as **this must be a different order number than the prenatal specimen.**

**Shipping Instructions**

Specimen preferred to arrive within 96 hours of collection.

**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, **but not required**, for this test. If proceeding with the prior authorization process, submit the required form with the specimen.

**Specimen Required**

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

**Submit only 1 of the following specimens:**

**Specimen Type:** Whole blood

**Container/Tube:**

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

**Acceptable:** Any anticoagulant

**Specimen Volume:** 3 mL

**Collection Instructions:**

- Invert several times to mix blood.
- Send whole blood specimen in original tube. **Do not aliquot.**

**Specimen Stability Information:** Ambient (preferred)/Refrigerated

**Prenatal Specimens**

**Due to its complexity, consultation with the laboratory is required for all prenatal testing;** call 800-533-1710 to speak to a genetic counselor.

**Specimen Type:** Amniotic fluid

**Container/Tube:** Amniotic fluid container

**Specimen Volume:** 20 mL

**Specimen Stability Information:** Refrigerated (preferred)/Ambient

**Additional information:**

- A separate culture charge will be assessed under CULAF / Culture for Genetic Testing, Amniotic Fluid.
- All prenatal specimens must be accompanied by a maternal blood specimen;** order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen.

**Specimen Type:** Chorionic villi

**Container/Tube:** 15-mL tube containing 15 mL of transport media

**Specimen Volume:** 20 mg

**Specimen Stability Information:** Refrigerated

**Additional Information:**

1. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 3 to 4 weeks is required to culture fibroblasts before genetic testing can occur.

2. **All prenatal specimens must be accompanied by a maternal blood specimen;** order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen.

**Acceptable:**

**Specimen Type:** Confluent cultured cells

**Container/Tube:** T-25 flask

**Specimen Volume:** 2 Flasks

**Collection Instructions:** Submit confluent cultured cells from another laboratory.

**Specimen Stability Information:** Ambient (preferred)/Refrigerated

**Additional Information:** **All prenatal specimens must be accompanied by a maternal blood specimen;** order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen.

**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 Panel \(NSRGG\) Prior Authorization Ordering Instructions](#)

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

**Specimen Minimum Volume**

Blood: 1 mL; Other specimen type: See Specimen Required

**Reject Due To**

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

**Specimen Stability Information**

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

**Clinical & Interpretive**

**Clinical Information**

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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 observed in NS 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.

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*. Variants in other genes on this panel have been associated with a smaller percentage of NS and related phenotypes, including Noonan syndrome with multiple lentigines (formerly known as LEOPARD syndrome), Noonan syndrome with loose anagen hair, cardiofaciocutaneous syndrome, Costello syndrome, Baraitser-Winter syndrome, and Legius syndrome.

### Reference Values

An interpretive report will be provided.

### Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.<sup>(1)</sup> Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

### Cautions

Clinical Correlations:

Test results should be interpreted in the 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 clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variant in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact the Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:

Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and

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repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

**Deletion/Duplication Analysis:**

This analysis targets single and multi-exon deletions/duplications; however, in some instances single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. For the most up to date list of genes included in this test and detailed information regarding gene specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

**Reclassification of Variants:**

At this time, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare providers to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time.

**Variant Evaluation:**

Evaluation and categorization of variants are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.<sup>(1)</sup> Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

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 periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Rarely, incidental or secondary findings may implicate another predisposition or presence of active disease. Incidental findings may include, but are not limited to, results related to the sex chromosomes. These findings will be carefully reviewed to determine whether they will be reported.

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**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;17(5):405-424.
2. Tartaglia M, Gelb BD, Zenker M, et al. Noonan syndrome and clinically related disorders. *Best Pract Res Clin Endocrinol Metab*. 2011;25(1):161-179
3. Romano AA, Allanson JE, Dahlgren J, et al. Noonan syndrome: clinical features, diagnosis, and management guidelines. *Pediatrics*. 2010;126(4):746–59
4. Roberts AE. Noonan syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews* [Internet]. University of Washington, 2007. Updated February 17, 2022. Accessed May 7, 2024. Available at [www.ncbi.nlm.nih.gov/books/NBK1124/](http://www.ncbi.nlm.nih.gov/books/NBK1124/)

**Performance****Method Description**

Next-generation sequencing (NGS) and/or Sanger sequencing are performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known disease-causing variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for deletion-insertions (delins) less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or a polymerase chain reaction-based quantitative method is performed to test for the presence of deletions and duplications in the genes analyzed.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. See [Targeted Genes and Methodology Details for Noonan Syndrome and Related Conditions Gene Panel](#) for details regarding the targeted genes analyzed for each test and specific gene regions not routinely covered. (Unpublished Mayo method)

Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

Genes analyzed: *ACTB*, *ACTG1*, *BRAF*, *CBL*, *HRAS*, *KRAS*, *LZTR1*, *MAP2K1*, *MAP2K2*, *MRAS*, *NRAS*, *PPP1CB*, *PTPN11*, *RAF1*, *RIT1*, *RRAS2*, *SHOC2*, *SOS1*, *SOS2*, and *SPRED1*.

**PDF Report**

Supplemental

**Day(s) Performed**

Varies

**Report Available**

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28 to 42 days

**Specimen Retention Time**

Whole blood: 2 weeks (if available); Extracted DNA: 3 months; Blood spots, saliva, cultured fibroblasts, skin biopsy, cord blood, amniotic fluid, cultured amniocytes, chorionic villi, cultured chorionic villi: 1 month

**Performing Laboratory Location**

Rochester

**Fees & 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 account representative. 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. It has not been cleared or approved by the US Food and Drug Administration.

**CPT Code Information**

81442

88233-Tissue culture, skin, solid tissue biopsy (if appropriate)

88240-Cryopreservation (if appropriate)

88235-Amniotic fluid culture (if appropriate)

81265-Maternal cell contamination (if appropriate)

**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
NSRGG	Noonan Syndrome and Related Panel	105199-4

Result ID	Test Result Name	Result LOINC® Value
617394	Test Description	62364-5
617395	Specimen	31208-2
617396	Source	31208-2
617397	Result Summary	50397-9



617398	Result	82939-0
617399	Interpretation	69047-9
617400	Additional Results	82939-0
617401	Resources	99622-3
617402	Additional Information	48767-8
617403	Method	85069-3
617404	Genes Analyzed	48018-6
617405	Disclaimer	62364-5
617406	Released By	18771-6