

# Noonan Spectrum Disorders Panel

Noonan spectrum disorders (NSD) are a group of genetic syndromes caused by pathogenic germline variants in genes in the Ras/mitogen activated protein kinase (MAPK) pathway, which controls the cell cycle and cell differentiation. The vast majority of causative variants increase pathway signaling; thus, the resulting syndromes exhibit phenotypic overlap and share a predisposition for developing malignancies.

## Disease Overview

### Symptoms of Noonan Syndrome (NS)

- Characteristic facial features
- Short stature
- Broad webbed neck (fetal cystic hygroma/increased nuchal translucency)
- Congenital heart defect
- Developmental delay
- Undescended testes
- Coagulation defects
- Lymphatic dysplasias

### Etiology of NSDs

Pathogenic sequence variants in Ras pathway genes

### Prevalence

NS: 1/1,000-2,500

### Inheritance

Autosomal dominant for all analyzed genes

### Genotype-Phenotype Correlation

Variants in multiple genes cause overlapping phenotypes for NSD

## Test Description

See [Genes Tested](#) table for genes included in this panel.

### Clinical Sensitivity

Dependent on clinical phenotype

- ~99% for cardiofaciocutaneous syndrome (CFCS)<sup>1</sup>
- ~80-90% for Costello syndrome (CS)<sup>2,3,4,5</sup>
- ~70-80% for NS<sup>6-13</sup>

### Limitations

- A negative result does not exclude a diagnosis of a MAPK pathway disorder.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if the individual has had an allogeneic stem cell transplantation.

## Tests to Consider

### [Noonan Spectrum Disorders Panel, Sequencing 2010772](#)

**Method:** Massively Parallel Sequencing

#### Ordering Indications

Confirm a suspected clinical diagnosis of:

- Noonan syndrome (NS)
- Cardiofacial cutaneous syndrome (CFCS)
- Costello syndrome (CS)
- Legius syndrome (LS)
- Noonan syndrome with multiple lentiginos (LEOPARD syndrome)
- Noonan-like syndrome
- Noonan-like syndrome with loose anagen hair (NS/LAH)

#### Contraindications

This panel should not be ordered in individuals with primary JMML as the assay may not detect mosaicism for somatic variants associated with malignancy.

#### Testing Strategy

Given the genotypic and phenotypic overlap among Noonan spectrum disorders (NSDs), the NSD panel is the recommended first-line test for determining a genetic etiology.

### [Noonan Spectrum Disorders Panel, Sequencing, Fetal 2010769](#)

**Method:** Massively Parallel Sequencing

#### Ordering Indications

Confirm a diagnosis of a NSD in a pregnancy with clinically suggestive findings, such as increased nuchal translucency, cystic hygroma, and cardiac defects.

#### Testing Strategy

For a fetus with ultrasonographic abnormalities, genomic microarray should be ordered prior to the NSD panel.

### [Familial Targeted Sequencing 3005867](#)

**Method:** Massively Parallel Sequencing

- Testing for a known familial sequence variant by sequencing gene of interest. A copy of the family member's test result documenting the familial gene variant is REQUIRED.
- To determine if the variant(s) of interest are detectable by this assay, contact an ARUP genetic counselor at 800-242-2787.

- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the targeted genes
  - Regulatory region variants and deep intronic variants
  - Large deletions/duplications
  - Noncoding transcripts
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants

## Analytic Sensitivity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate <sup>a</sup> (%)	Analytical Sensitivity (PPA) 95% Credibility Region <sup>a</sup> (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	100	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	100	62.1-100

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

## Genes Tested

Gene	Alias Symbol(s)	MIM Number	Disorder
<i>BRAF</i>	BRAF1	164757	CFCS 1 NS 1 NS 7 LEOPARD syndrome 3
<i>CBL</i>	CBL2, RNF55, c-Cbl	165360	NS-like disorder with or without juvenile myelomonocytic
<i>HRAS</i>	HRAS1	190020	Melanocytic Nevus syndrome, congenital Schimmelpenning-Feuerstein-Mims syndrome CS
<i>KRAS</i>	KRAS2, KRAS1	190070	Schimmelpenning-Feuerstein-Mims syndrome NS 3 CFCS 2
<i>LZTR1</i>	LZTR-1, BTBD29	600574	NS 10
<i>MAP2K1</i>	PRKMK1, MEK1, MAPKK1	176872	NS 1 CFCS 3
<i>MAP2K2</i>	PRKMK2, MEK2	601263	CFCS 4
<i>NRAS</i>	N-ras	164790	Schimmelpenning-Feuerstein-Mims syndrome NS 6

Gene	Alias Symbol(s)	MIM Number	Disorder
<i>PTPN11</i>	NS1, BPTP3, SH-PTP2, SHP-2, PTP2C, SHP2	176876	LEOPARD syndrome 1 NS 1
<i>RAF1</i>	Raf-1, c-Raf, CRAF	164760	NS 5 LEOPARD syndrome 2
<i>RASA2</i>	GAP1M	601589	
<i>RIT1</i>	RIT, RIBB, ROC1, MGC125864, MGC125865	609591	NS 8
<i>SHOC2</i>	KIAA0862, SOC2, SUR-8, SOC-2, SUR8	602775	NS-like disorder with loose anagen hair 1
<i>SOS1</i>	GINGF, HGF, GF1	182530	NS 4
<i>SOS2</i>		601247	NS 9
<i>SPRED1</i>	FLJ33903, PPP1R147	609291	Legius syndrome

## References

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## Related Information

[Laboratory Testing for Developmental Delay, Intellectual Disability, and Autism Spectrum Disorder](#)  
[Testing for Genetic Syndromes Related to Developmental Delay \(DD\), Intellectual Disability \(ID\), and Autism Spectrum Disorder \(ASD\)](#)

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