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 NSD**
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)\(^1\)
- ~80-90% for Costello syndrome (CS)\(^2,3,4,5\)
- ~70-80% for NS\(^6,7,8,9,10,11,12,13\)

**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.

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**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 lentigines (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.
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:

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

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

### Genes Tested

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alias Symbol(s)</th>
<th>MIM Number</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRAF</strong></td>
<td>BRAF1</td>
<td>164757</td>
<td>CFCS 1 NS 1 NS 7 LEOPARD syndrome 3</td>
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<tr>
<td><strong>CBL</strong></td>
<td>CBL2, RNF55, c-Cbl</td>
<td>165360</td>
<td>NS-like disorder with or without juvenile myelomonocytic</td>
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<td><strong>HRAS</strong></td>
<td>HRAS1</td>
<td>190020</td>
<td>Melanocytic Nevus syndrome, congenital Schimmelpenning-Feuerstein-Mims syndrome CS</td>
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<td><strong>KRAS</strong></td>
<td>KRAS2, KRAS1</td>
<td>190070</td>
<td>Schimmelpenning-Feuerstein-Mims syndrome NS 3 CFCS 2</td>
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<td><strong>LZTR1</strong></td>
<td>LZTR-1, BTBD29</td>
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<td>NS 10</td>
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<td><strong>MAP2K1</strong></td>
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<td><strong>MAP2K2</strong></td>
<td>PRKMK2, MEK2</td>
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<td>CFCS 4</td>
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<td><strong>NRAS</strong></td>
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<td>Schimmelpenning-Feuerstein-Mims syndrome NS 6</td>
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<td><strong>PTPN11</strong></td>
<td>NS1, BPTP3, SH-PTP2, SHP-2, PTP2C, SHP2</td>
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<td>LEOPARD syndrome 1 NS 1</td>
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<td><strong>RAF1</strong></td>
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<td>NS 5 LEOPARD syndrome 2</td>
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<td><strong>RASA2</strong></td>
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<td><strong>RIT1</strong></td>
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<td>Gene</td>
<td>Alias Symbol(s)</td>
<td>MIM Number</td>
<td>Disorder</td>
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<td>SHOC2</td>
<td>KIAA0862, SOC2, SUR-8, SOC-2, SUR8</td>
<td>602775</td>
<td>NS-like disorder with loose anagen hair 1</td>
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<td>SOS1</td>
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<td>SOS2</td>
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<td>601247</td>
<td>NS 9</td>
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<td>SPRED1</td>
<td>FLJ33903, PPP1R147</td>
<td>609291</td>
<td>Legius syndrome</td>
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</tbody>
</table>

REFERENCES


RELATED INFORMATION
ARUP Consult® Algorithm

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

RELATED TESTS

Noonan Syndrome (PTPN11) Sequencing with Reflex to (SOS1) Sequencing 2004189
Method: Polymerase Chain Reaction/Sequencing

Noonan Syndrome (PTPN11) Sequencing 0051805
Method: Polymerase Chain Reaction/Sequencing

Noonan Syndrome (SOS1) Sequencing 2004195
Method: Polymerase Chain Reaction/Sequencing

Familial Mutation, Targeted Sequencing 2001961
Method: Polymerase Chain Reaction/Sequencing