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)\(^1\)
- ~80-90% for Costello syndrome (CS)\(^2,3,4,5\)
- ~70-80% for NS\(^6-13\)

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.

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.

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:

<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>
</tr>
<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>
</table>
| BRAF    | BRAF1                 | 164757     | CFCS 1
         |                       |            | NS 1
         |                       |            | NS 7
<pre><code>     |                       |            | LEOPARD syndrome 3    |
</code></pre>
<p>| CBL     | CBL2, RNF55, c-Cbl    | 165360     | NS-like disorder with or without juvenile myelomonocytic                |
| HRAS    | HRAS1                 | 190020     | Melanocytic Nevus syndrome, congenital                                   |
|         |                       |            | Schimmelpenning-Feuerstein-Mims syndrome                                 |
|         |                       |            | CS                                                                       |
| KRAS    | KRAS2, KRAS1          | 190070     | Schimmelpenning-Feuerstein-Mims syndrome                                 |
|         |                       |            | NS 3                                                                    |
|         |                       |            | CFCS 2                                                                  |
| LZTR1   | LZTR-1, BTBD29        | 600574     | NS 10                                                                   |
| MAP2K1  | PRKMK1, MEK1, MAPKK1  | 176872     | NS 1                                                                    |
|         |                       |            | CFCS 3                                                                  |
| MAP2K2  | PRKMK2, MEK2          | 601263     | CFCS 4                                                                  |
| NRAS    | N-ras                 | 164790     | Schimmelpenning-Feuerstein-Mims syndrome                                 |
|         |                       |            | NS 6                                                                    |</p>
<table>
<thead>
<tr>
<th>Gene</th>
<th>Alias Symbol(s)</th>
<th>MIM Number</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTPN11</td>
<td>NS1, BPTP3, SH-PTP2, SHP-2, PTP2C, SHP2</td>
<td>176876</td>
<td>LEOPARD syndrome 1</td>
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<td>RAFl</td>
<td>Raf-1, c-Raf, CRAF</td>
<td>164760</td>
<td>NS 5</td>
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<td>RASA2</td>
<td>GAP1M</td>
<td>601589</td>
<td>LEOPARD syndrome 2</td>
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<td>RIT1</td>
<td>RIT, RIBB, ROC1, MGC125864, MGC125865</td>
<td>609591</td>
<td>NS 8</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>
<td>GINGF, HGF, GF1</td>
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<td>NS 4</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>FLJ39303, PPP1R147</td>
<td>609291</td>
<td>Legius syndrome</td>
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</tbody>
</table>

References


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)