Noonan syndrome is a genetically heterogeneous condition which overlaps with a spectrum of other disorders, including cardio-facio-cutaneous (CFC) syndrome, LEOPARD syndrome, and Costello syndrome. Clinical features of Noonan spectrum disorders include short stature, cardiovascular disease (pulmonary valve stenosis and hypertrophic cardiomyopathy), characteristic facies, and developmental delay. Findings in the hematologic, skeletal, and cutaneous systems can also be associated with the spectrum of disorders. All of the Noonan spectrum disorders demonstrate autosomal dominant inheritance.

**Noonan syndrome**
Noonan syndrome is characterized by short stature, cardiovascular disease, and a varying degree of developmental delay. Common findings in Noonan syndrome include broad/webbed neck, chest wall abnormalities, cryptorchidism, characteristic facies, coagulation problems, ocular abnormalities, and lymphatic dysplasias. The diagnosis of Noonan syndrome can be made through clinical assessment. Mutations in \textit{PTPN11} account for approximately 50% of cases of Noonan syndrome, however mutations in \textit{SOS1}, \textit{RAF1}, \textit{KRAS}, \textit{NRAS}, and \textit{SHOC2} have also been reported.

**Cardio-Facio-Cutaneous (CFC) syndrome**
CFC syndrome is characterized by cardiac, ectodermal abnormalities and characteristic facies. Cardiac findings can include pulmonary valve stenosis or other valve dysplasias, septal defects, hypertrophic cardiomyopathy, and rhythm disturbances. Other common features include sparse, curly or slow-growing hair, and skin abnormalities such as atopic dermatitis and hyperkeratosis with ichthyosis-like lesions. Mild to severe intellectual disability is seen in the majority of individuals with CFC syndrome. Mutations in \textit{BRAF} account for approximately 75% of cases of CFC syndrome, however mutations in \textit{MAP2K1}, \textit{MAP2K2}, and \textit{KRAS} have also been reported.

**LEOPARD syndrome**
LEOPARD syndrome is an acronym for the cardinal features (Lentigines, ECG conduction abnormalities, Ocular hypertelorism, Pulmonic stenosis, Abnormal genitalia, Retardation of growth, and sensorineural Deafness). Mutations in \textit{PTPN11} (mainly exons 7, 12, and 13) have been detected in the majority of cases of LEOPARD syndrome, however mutation in \textit{RAF1} have also been reported.

**Costello syndrome**
Costello syndrome is characterized by failure to thrive due to postnatal feeding difficulties, short stature, developmental delay, skeletal anomalies, typical craniofacial features, cardiac abnormalities, and an increased risk for malignant tumors. Cardiac findings can include pulmonary valve stenosis, septal defects, hypertrophic cardiomyopathy, or rhythm disturbances. Coarse facial features can be seen, as well as, curly or sparse hair and hypertonia. Specific sequence variants in the \textit{HRAS} gene are associated with Costello syndrome.

**Indication**
The Noonan Spectrum Panel is indicated for individuals with clinical suspicion for a Noonan spectrum disorder.
Methodology:

Next Generation Sequencing: All coding exons, as well as their flanking regions, of the genes listed in the panel are enriched from the patient’s genomic DNA and sequenced using a solid-state sequencing-by-synthesis process. DNA sequences are assembled and compared to the published genomic reference sequences in Genome Reference Consortium Build 37. Dideoxy DNA sequencing is used to provide data for bases with insufficient coverage and to confirm the reported variants from next-generation sequencing. This assay does not detect variants in the promoter regions, deep intronic regions, or other regulatory elements, and does not detect large deletions or mosaics. Variants are reported according to HGVS nomenclature (www.hgvs.org/mutnomen).

Validation testing indicates an analytic sensitivity of greater than 99.8% and an analytic specificity of 100%.

Based on the literatures, the clinical validity is determined to be:
- 71%-88% for Noonan syndrome
- Greater than 95% for LEOPARD syndrome
- Greater than 99% for CFC syndrome
- 80-90% for Costello syndrome

References:


CPT Codes:

Panel: 81404 x2, 81405 x2, 81406 x6, 81408, 81479 x2
Known Mutation Testing: 81403

<table>
<thead>
<tr>
<th>Noonan Syndrome Genes</th>
<th>Known Mutation Testing</th>
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<tr>
<td>PTPN11, RAF1</td>
<td>Panel: 81404 x2, 81405 x2, 81406 x6, 81408, 81479 x2</td>
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<tr>
<td>SOS1, MAP2K1</td>
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<td>KRAS, NRAS</td>
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<td>BRAF, SHOC2</td>
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<td>NF1, MAP2K2</td>
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<td>CBL, HRAS</td>
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Specimen:

Peripheral blood in EDTA tube
Adult: 3-5mL
Child: 3-5mL
Infant: 1-3mL
For other specimen types, please contact Amy Shikany at 513-803-3317

Turnaround Time:

Full Mutation Analysis 8-10 weeks
Known Mutation Analysis 1-2 weeks