

Noonan Syndrome via Sequential *PTPN11*, *RAF1*, *SOS1* and *KRAS* Gene Sequencing

Sequential (Standard) Test – Test #370; Tier 1 Only – Test #371; Tier 2 Only – Test #372

Brief Description of Disorder: Noonan Syndrome (NS) (OMIM 163950) is a relatively common dysmorphic syndrome characterized by short stature, heart defects, broad or webbed neck, and characteristic facial features (Tartaglia and Gelb Ann Rev Genomics Hum Genet 6:45-68, 2005; Allanson Gene Reviews, 2007; van der Burgt Orphanet J Rare Diseases 2:4, 2007). A number of other symptoms are sometimes observed including mild mental retardation and ectodermal features. Symptoms are quite variable even among family members carrying the same mutation. Diagnosis is often made in infancy or early childhood. Prevalence is roughly 1 in 2000 births. Symptoms often lessen with advancing age. See also the Noonan Syndrome Support Group, Inc. (www.noonansyndrome.org).

Genetics: NS is an autosomal dominant disorder, although *de novo* mutations are found in a substantial fraction of patients. Mutations in *PTPN11*, *SOS1*, *RAF1* and *KRAS* genes have been reported to be causative for NS. See individual test descriptions of these genes for references and more information. About 50% of NS patients carry causative mutations in *PTPN11*, about 10% have mutations in *SOS1*, perhaps 10% mutations in *RAF1* (data are sparse) and 2% mutations in *KRAS*. Nearly all causative mutations reported to date in these genes have been missense resulting in amino acid substitutions. Genotype-phenotype correlations for NS are just beginning to be made.

Description of This Particular Test: PreventionGenetics offers sequencing of each of the four genes individually, or the Sequential Test described here. The Sequential Test has two Tiers and offers substantial cost savings over individual gene sequencing. Tier 1 involves sequencing of exons 3, 7, 8, and 13 of *PTPN11*. These four exons contain about 45% of causative NS mutations. If Tier 1 is negative, we go on to Tier 2 which involves sequencing of the remaining 11 exons of *PTPN11*, exons 7, 14 and 17 of *RAF1*, all 23 exons of *SOS1*, and all 4 exons of *KRAS*. Tiers 1 and 2 together bring the total detection rate up to roughly 70%. The two Tiers may be ordered separately.

Reference Sequences:

| Gene: | Genomic: | mRNA: | Protein: |
|---------------|--------------|-------------|-------------|
| <i>PTPN11</i> | NC_000012.10 | NM_002834.3 | NP_002825.3 |
| <i>RAF1</i> | NC_000003.10 | NM_002880.2 | NP_002871.1 |
| <i>SOS1</i> | NC_000002.10 | NM_005633.2 | NP_005624.2 |
| <i>KRAS</i> | NC_000012.10 | NM_004985.3 | NP_004976.2 |

Indications for Test: Candidates for this test are patients with symptoms consistent with a diagnosis of Noonan Syndrome. Symptoms of NS patients overlap with those for Cardio-Facio-Cutaneous (CFC) and Costello Syndromes. Testing of the CFC (*BRAF*, *MAP2K1*, *MAP2K2*) and Costello (*HRAS*) genes in patients who are negative for Noonan testing should therefore be considered.

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form

Prices: Tier 1 alone \$390 Tier 2 alone \$1990 Tiers 1 and 2 together \$1990

| CPT Codes | Description | Tier1 only | Tier 2 only | Tier 1 + Tier 2 together |
|----------------|------------------------------|--------------|---------------|--------------------------|
| 83890 | Ascertainment | \$ 30 (x1) | \$ 30 (x1) | \$ 30 (x1) |
| 83891 | DNA Isolation | \$ 40 (x1) | \$ 40 (x1) | \$ 40 (x1) |
| 83898 | Amplification | \$100 (x4) | \$690 (x38) | \$690 (x42) |
| 83904 | Mutation Ident by Sequencing | \$140 (x4) | \$1040 (x38) | \$1040 (x42) |
| 83894 | Separation | \$ 20 (x1) | \$ 80 (x1) | \$ 80 (x1) |
| 83912 | Interpretation and Report | \$ 60 (x1) | \$110 (x1) | \$110 (x1) |
| Totals: | | \$390 | \$1990 | \$1990 |

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

Contact for info: Dr. Khemissa Bejaoui, khemissa@preventiongenetics.com, www.preventiongenetics.com