

Noonan Syndrome via *SOS1* Gene Sequencing (Test #376)

Brief Description of Disorder: Noonan Syndrome (NS) (OMIM 163950) is a relatively common developmental disorder 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. Causative mutations have been reported in four genes: *PTPN11*, *RAF1*, *SOS1* and *KRAS*. Roughly 10% of NS patients (~20% of those who are *PTPN11* mutation negative) carry mutations in the *SOS1* gene (Roberts et al. Nat Genet 39:70-74, 2007; Tartaglia et al. Nat Genet 39:75-79, 2007; Zenker et al. J Med Genet 44:651-656, 2007). All causative *SOS1* mutations reported to date have been missense resulting in amino acid substitutions. Initial indications are that NS patients with normal growth, ectodermal features, and curly hair are more likely to have *SOS1* than *PTPN11* mutations. These distinctions are not absolute however.

Description of This Particular Test: Testing of the *SOS1* gene for NS is performed at PreventionGenetics in two tiers. In Tier 1, we bidirectionally sequence the complete coding regions plus about 50 bp of flanking DNA on each side of exons 3, 6-8, 10-11, 13-14 and 16. These nine exons contain all (current) reported causative mutations. If Tier 1 is negative, we go on to sequence the remaining 14 exons in Tier 2. PreventionGenetics also offers sequencing of the *PTPN11*, *RAF1* and *KRAS* genes.

Reference Sequences: Genomic: **NC_000002.10** mRNA: **NM_005633.2** protein: **NP_005624.2**

Indications for Test: Candidates for this test are patients with symptoms consistent with a diagnosis of Noonan Syndrome, particularly those with negative *PTPN11* tests. Symptoms of NS patients overlap with those for Cardio-Facio-Cutaneous (CFC) and Costello Syndrome patients. NS patients who test negative for the mutations in *PTPN11*, *RAF1*, *SOS1* or *KRAS* may be candidates for CFC (*BRAF*, *MEK1*, and *MEK2* genes) or Costello (*HRAS* gene) testing. Conversely, CFC or Costello Syndrome patients who test negative for *BRAF*, *MEK1*, *MEK2* and *KRAS* genes or *HRAS*, respectively, may be candidates for all or a portion of our NS testing.

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

Prices: Tier 1 only **\$590** Tiers 1 and 2 **\$1190**

CPT Codes:

Codes	Description	Tier 1 Only	Tier 1 + Tier 2
83890	Ascertainment	\$ 30 (x1)	\$ 30 (x1)
83891	DNA Isolation	\$ 40 (x1)	\$ 40 (x1)
83898	Amplification	\$160 (x9)	\$380 (x23)
83904	Mutation Ident by Sequencing	\$230 (x9)	\$560 (x23)
83894	Separation	\$ 50 (x1)	\$ 70 (x1)
83912	Interpretation and Report	\$ 80 (x1)	\$110 (x1)
Totals:		\$590	\$1190

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

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