

Noonan, CFC and Costello Syndromes via *KRAS* Gene Sequencing (Test #378)

Brief Description of Disorder: Noonan Syndrome (NS) (OMIM 163950) and Cardio-Facio-Cutaneous (CFC) Syndrome (OMIM 115150) are developmental disorders with overlapping clinical features and overlapping genetics. Noonan Syndrome is a relatively common dysmorphic 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 including mild mental retardation and ectodermal features are sometimes observed. 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. See also the Noonan Syndrome Support Group, Inc. (www.noonansyndrome.org).

Cardio-Facio-Cutaneous (CFC) Syndrome is characterized by distinctive facial appearance, skin abnormalities, heart malformations and/or mental retardation. Dysmorphic features may include: macrocephaly with bitemporal constriction, a short, upturned nose with a low nasal bridge, and/or prominent external ears that are posteriorly angulated. Affected individuals may also have palpebral fissures, ocular hypertelorism, ptosis, esotropia, and other eye abnormalities. CFC patients may have dry, brittle, curly scalp hair, and often lacks eyebrows and eyelashes. For further information see <http://www.cfcsyndrome.org/> and Reynolds et al. Am J Med Genet 25:413-427, 1986.

Genetics: NS and CFC Syndromes are autosomal dominant disorders, although *de novo* mutations are found in a substantial fraction of NS patients and virtually all CFC patients. Mutations in the *PTPN11*, *SOS1*, *RAF1* and *KRAS* genes have been reported to be causative for NS. Roughly 50% of NS patients carry causative mutations in *PTPN11*. Of the remainder, perhaps 7% have mutations in *SOS1* and 2% in *KRAS*.

Description of This Particular Test: This test involves bidirectional DNA sequencing of all coding exons of the *KRAS* gene. The full coding region of each exon plus ~50 bp of flanking non-coding DNA on either side are sequenced. We will sequence any single exon in family members of patients with known mutations, and to confirm research results (\$190).

Reference Sequences: Genomic: NC_000012.10 mRNA: NM_004985.3 protein: NP_004976.2

Indications for Test: All NS and CFC Syndrome patients that are negative for mutations in the primary genes (*PTPN11* and *BRAF*) are candidates for this test.

Sensitivity of Test: As described above under **Genetics**, a small, but significant fraction of NS and CFC Syndrome patients have *KRAS* mutations.

Turn Around Time: Maximum of 40 days, although many of these tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of exons 2, 3, 4 and 6 of *KRAS* Gene \$ 440

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x4	83898	\$ 110	Sequencing x4	83904	\$ 160
Separation	83894	\$ 30	Interpretation/Report	83912	\$ 70

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

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