Noonan Spectrum Disorders
Sequencing Panel

Noonan Spectrum Disorders, or RASopathies, are genetically heterogeneous developmental syndromes caused by germline mutations in genes involved in the Ras/MAPK signaling pathway. This pathway is essential in the regulation of cell cycle, differentiation and growth. The prevalence of the Noonan Spectrum Disorders is between 1 in 1,000 and 1 in 2,500 live births. Performing genetic testing can be clinically useful postnatally for individuals that display characteristic features *(cardiac abnormalities, developmental delay/intellectual disability, etc)*, or prenatally for fetuses that present with certain ultrasound findings *(cystic hygroma, increased nuchal translucency, etc)* after a normal chromosome analysis. The 14 genes targeted in this sequencing panel are detailed in the table below.

Syndrome	Common Phenotypic Traits	Gene(s)	Molecular Diagnostic Rate*
Noonan syndrome (NS)	Short stature, congenital heart defects (CHD), hypertrophic cardiomyopathy (HCM), developmental delay (DD), skeletal anomalies, webbed neck, facial dysmorphisms, cryptorchidism in males, bleeding diathesis, lymphatic dysplasias, increased risk of malignancy, childhood predisposition to JMML	*PTPN11, KRAS, SOS1, RAF1, NRAS, BRAF, MAP2K1, CBL, RIT1*	64%-86%
LEOPARD syndrome	Short stature, CHD and conduction abnormalities, intellectual disability (ID), facial dysmorphisms, sensorineural deafness, skin lentigines	*PTPN11, RAF1, BRAF*	~90%
Costello syndrome	Short stature, CHD, ID, coarse facies, macrocephaly, postnatal feeding difficulties, musculoskeletal and skin abnormalities, sparse/fine hair, progressive cerebellar overgrowth, increased risk of malignancy	*HRAS*	80%-90%
Cardiofaciocutaneous syndrome (CFC)	Short stature, CHD, ID, coarse facies, severe feeding problems, abnormalities of the skin and hair, increased risk of malignancy	*BRAF, MAP2K1, MAP2K2, KRAS*	>62%
Noonan-like syndrome with loose anagen hair	Short stature, CHD, easily-pluckable, sparse, thin, and slow-growing hair (loose anagen hair), skin abnormalities, hypernasal voice, distinctive hyperactive behavior, ID	*SHOC2*	~100%
Neurofibromatosis type 1 (NF1), Neurofibromatosis-Noonan syndrome	Short stature, learning disability, multiple café au lait, axillary, inguinal freckling, neurofibromas, iris Lisch nodules, facial dysmorphisms, macrocephaly, increased risk of malignancy	*NF1, SPRED1, PTPN11*	~90%

** Molecular diagnostic rate for postnatal specimens. The clinical sensitivity of this test for prenatal samples has not been established yet.*

Genetics:

Noonan Spectrum Disorders are inherited in an autosomal dominant manner. This means that a parent carrying a mutated gene has a 50% chance of passing it on to an offspring, regardless of gender. Some of these genes are not fully penetrant (an individual may have a mutated gene but not display any of the signs/symptoms of the disorder). Additionally, these disorders have variable expressivity (individuals with the same diagnosis may display differing features and differing severity of symptoms).

A person can harbor a mutation from one of two sources:

- either the person inherited this mutation from an affected (or unaffected, non-penetrant) parent
- or the mutation was a "*de novo*" DNA change that occurred in the egg or sperm from which the affected individual developed. Rarely, a mutation may occur post-zygotically and may not be present in every cell in the body (mosaicism).

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Testing Methods:

DNA is obtained from a blood (postnatal) sample or a prenatal specimen (direct or cultured Chorionic Villus Sampling or amniocytes). High-throughput, next generation sequencing is performed to examine several genes at one time. In addition, some of the genes on the panel may be partially subjected to Sanger sequencing due to inadequate sequence coverage by next generation sequencing.

Test Sensitivity and Limitations:

Technological and analytical test sensitivity of next generation sequencing used for this panel is 99% for detecting substitutions and 95% for detection small insertion and deletions. Larger genomic rearrangements and DNA insertions or deletions will likely be missed by this testing method. Untranslated regions (UTRs) and gene promoter regions are not tested. However, nearly all reported pathogenic mutations causing Noonan spectrum disorders have been missense mutations in coding regions (with the exception of *NF1* mutations). Nevertheless, patients with negative test results may still have a mutation in one of the genes on the panel that was not identified by this testing or may have a mutation(s) in a gene not included in this panel.

In the prenatal setting, it has been reported that 9% of fetuses with abnormal ultrasound findings, including abnormal nuchal translucency and cystic hygroma, were found to have mutations in *PTPN11* (PMID 18759865)[i]. In a recent study, mutations were identified in three out of four NS genes (*PTPN11, RAF1, and KRAS*) that were sequenced in fetuses with a normal karyotype and abnormal ultrasound findings. The detection rate in this study was 17.3%. (PMID23321623)[ii].

Turnaround Time:

Results are reported to the referring physician within 3-4 weeks for prenatal cases and 6-8 weeks for postnatal cases from the receipt of the specimen.

Specimen and Shipping Requirements:

For postnatal cases: 2 yellow-top (ACD-A or ACD-B) or 2 lavender-top (EDTA), 5-10 ml tubes of blood from the patient and both of his/her parents are required.

For prenatal cases: 2 confluent T-25 flasks of cultured cells (originating from amniotic fluid or chorionic villi) or more than 4 mg of direct CVS tissue, or 15 ml of direct amniotic fluid (AF) as well as 2 lavender-top (EDTA), 5-10 ml tubes of blood from the pregnant patient and her partner are required.

Note: *Parental blood samples are requested for confirmation studies necessary in some cases; maternal blood is also used for maternal cell contamination studies.*

Tubes of blood, cultured cells, direct CVS, and direct AF should be kept and shipped refrigerated or at room temperature (*please do NOT freeze*).

References:

i. *Lee KA, et al. PTPN11 analysis for the prenatal diagnosis of Noonan syndrome in fetuses with abnormal ultrasound findings. Clin Genet. 2009 Feb;75(2):190-4*

ii. *Croonen EA, et al. Prenatal diagnostic testing of the Noonan syndrome genes in fetuses with abnormal ultrasound findings. Eur J Hum Genet. 2013 Sep;21(9):936-42.*

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