

Heart Institute Diagnostic Lab

CAP#: 1667801

CLIA#: 36D0656333

Phone: (513) 803-1751

Fax: (513) 803-1748

Email: HeartDx@cchmc.org

Shipping Instructions

Please enclose a test requisition form with sample. All information must be complete before sample can be processed. Samples may be shipped at room temperature by overnight Federal Express to arrive Monday through Friday.

Ship To:

Cincinnati Children's
Hospital Medical Center

Attn: Heart Institute Diagnostic Lab

240 Albert Sabin Way,
Room S4.381

Cincinnati, OH 45229-3039

Noonan Spectrum Panel

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 *PTPN11* account for approximately 50% of cases of Noonan syndrome, however mutations in *SOS1*, *RAF1*, *KRAS*, *NRAS*, and *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 *BRAF* account for approximately 75% of cases of CFC syndrome, however mutations in *MAP2K1*, *MAP2K2*, and *KRAS* have also been reported.

LEOPARD syndrome

LEOPARD syndrome is an acronym for the cardinal features (**L**entigines, **E**CG conduction abnormalities, **O**cular hypertelorism, **P**ulmonic stenosis, **A**bnormal genitalia, **R**etardation of growth, and **D**eafness). Mutations in *PTPN11* (mainly exons 7, 12, and 13) have been detected in the majority of cases of LEOPARD syndrome, however mutation in *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 *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 mosaicisms. Variants are reported according to HGVS nomenclature (www.hgvs.org/mutnomen).

Sensitivity & Accuracy:

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:

1. Allanson J, Roberts A. Noonan Syndrome. 2001 Nov 15 [Updated 2011 Aug 4]. In: Pagon RA, Adam MP, Bird TD, et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993.
2. Gelb B, Tartaglia M. LEOPARD Syndrome. 2007 Nov 30 [Updated 2010 Nov 16]. In: Pagon RA, Adam MP, Bird TD, et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993.
3. Rauen K. Cardiofaciocutaneous Syndrome. 2007 Jan 18 [Updated 2012 Sep 6]. In: Pagon RA, Adam MP, Bird TD, et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993.
4. Gripp K, Lin A. Costello Syndrome. 2006 Aug 29 [Updated 2012 Jan 12]. In: Pagon RA, Adam MP, Bird TD, et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993.

CPT Codes:

Noonan Syndrome Genes	
PTPN11,	RAF1
SOS1,	MAP2K1
KRAS,	NRAS
BRAF,	SHOC2
NF1,	MAP2K2
CBL,	HRAS

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

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