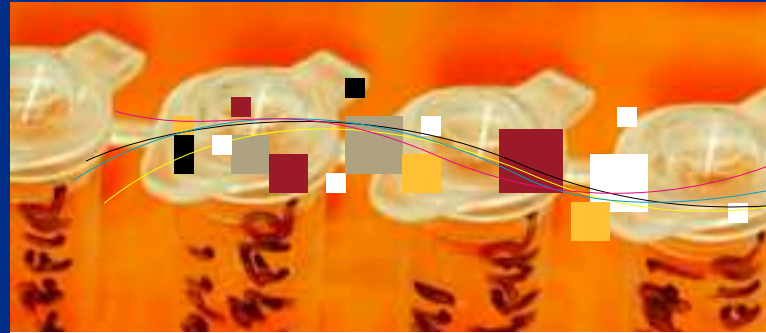


## LABORATORY FOR MOLECULAR MEDICINE



### HARVARD MEDICAL SCHOOL-PARTNERS HEALTHCARE CENTER FOR GENETICS AND GENOMICS



## TESTING FOR NOONAN, LEOPARD, CARDIO-FACIO CUTANEOUS, AND COSTELLO SYNDROMES

Complete gene sequencing  
assays for members of the  
Ras/Raf/MEK/ERK signal  
transduction pathway

Did you know that mutations  
in four different genes can  
cause Noonan Syndrome?



## About the Laboratory

The Laboratory for Molecular Medicine (LMM) is a nonprofit CLIA-certified clinical diagnostic laboratory of the Harvard Medical School-Partners HealthCare Center for Genetics and Genomics. The LMM's close connection to the research community and access to cutting-edge technology ensures rapid translation of discoveries into clinical tests offered by the laboratory.

**Director:** Raju Kucherlapati, PhD

### More Information

Please contact the LMM for more information about ordering our tests, sending a sample, payment options, and research opportunities.

### Laboratory for Molecular Medicine

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Web: [www.hpcgg.org/imm](http://www.hpcgg.org/imm)

### Affiliated clinical genetics services for Noonan, LEOPARD, CFC and Costello syndromes:

#### Children's Hospital Boston *Cardiovascular Genetics Clinic*

Amy Roberts, M.D., FACMG  
300 Longwood Ave  
Boston, MA 02115  
To schedule an appointment call 617-355-2079

### Privacy

The LMM is dedicated to ensuring the privacy and confidentiality for all individuals who decide to pursue genetic testing.

## Noonan Syndrome

Noonan Syndrome (NS) is one of the most common conditions associated with a congenital heart abnormality, with 1/1000 to 1/2500 children affected. However, NS may be underdiagnosed and these estimates may be low.

For individuals with short stature, congenital heart disease (most commonly pulmonary valve disease or hypertrophic cardiomyopathy), learning problems or developmental delays, webbed neck, and/or widely spaced eyes, a diagnosis of NS should be considered.

As an autosomal dominant disorder, each child of an individual with NS has a 50% (or 1 in 2) chance of inheriting the condition (Image 1: Left). Unaffected parents may also have a child with NS due to a sporadic mutation (Image 1: Right)

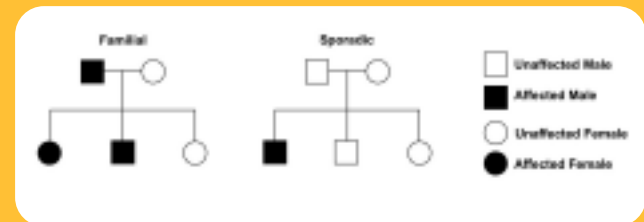


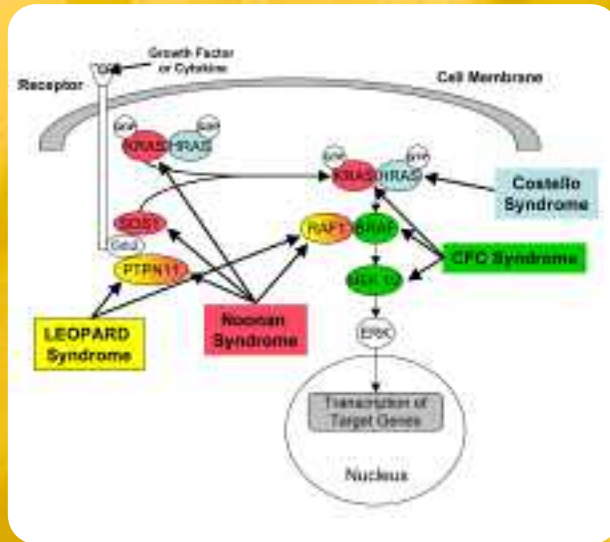
Image 1: Pedigree

## Genetic Testing for Noonan Syndrome

Mutations in *PTPN11* have been detected in about 50% of individuals clinically diagnosed with NS. A large majority of these *PTPN11* mutations cluster within certain areas of the gene (exons 3, 8, and 13). Mutations in several other genes can also cause NS. Approximately 10% of individuals with NS have mutations in *SOS1*, 3-17% have mutations in *RAF1*, and 1% have mutations in *KRAS*.

*PTPN11*, *SOS1*, *RAF1* and *KRAS* are all components of the Ras/Raf/MEK/ERK signal transduction pathway. This pathway is important in the regulation of cell growth (Image II) and mutations in these genes are responsible for a variety of syndromes including NS.

Image II: Ras/Raf/MEK/ERK Signal Transduction Pathway.



## Genetic Testing for Noonan Syndrome:

### Gene Sequencing Noonan syndrome Detection Rate

- *PTPN11* (exons 3, 8 & 9, 13) 45%
- *SOS1* (exons 1-23) 10%
- *RAF1* (exons 1-17) 3-17%
- *PTPN11* (exons remaining) and *KRAS* (exons 1-6) 6%

Individual gene sequencing tests are also available.

### Prenatal testing is available for all tests.

### Familial Known Mutation Test

Sequence analysis of a single exon in *PTPN11*, *SOS1*, *RAF1* or *KRAS* to determine the presence or absence of a known mutation, previously detected in an affected family member.

### Benefits of Testing

Identification of mutations in *PTPN11*, *SOS1*, *RAF1* or *KRAS* establishes the molecular genetic cause for a clinical diagnosis of NS. Knowledge of a causative mutation allows parents and siblings to be tested. An affected parent is recognized about half of the time when a child is diagnosed.

Children found to have a mutation should be followed for the potential medical issues associated with NS including visual problems, bleeding problems, lymphatic abnormalities, renal anomalies, developmental delay, and cardiovascular abnormalities.

If an adult has a mutation they can use that information to make informed family planning decisions.

### Limitations of Testing

Failure to identify a mutation by these sequencing tests will not exclude the diagnosis of NS.

## Test Indications

- Patients who have clinical features associated with NS
- Parents of a fetus or child diagnosed with NS
- Prenatal testing when a parent or first degree relative has been diagnosed with NS
- Prenatal diagnosis for a fetus with increased nuchal translucency and/or cystic hygroma and a normal chromosome analysis

## Clinical Features

Individuals with NS may have some or all of the following findings:

- Characteristic facial features: drooping upper eyelids (ptosis), widely spaced downslanting eyes, low set ears, triangular face
- Congenital heart defect: most commonly pulmonic valve stenosis or hypertrophic cardiomyopathy
- Short stature
- Developmental delay of variable degree
- Broad or webbed neck
- Apparently widely-spaced nipples; caved in or convex chest (pectus excavatum/carinatum)
- Undescended testes (cryptorchidism)
- Predisposition to malignancy

## Syndromes with clinical overlap with Noonan Syndrome

LEOPARD Syndrome is also caused by mutations in *PTPN11* and *RAF1*. LEOPARD is an acronym used to describe the constellation of symptoms seen in affected individuals:

- L – Multiple Lentigenes (dark skin spots)
- E – Electrocardiographic conduction abnormalities
- O – Ocular hypertelorism (widely spaced eyes)
- P – Pulmonic stenosis
- A – Abnormal genitalia
- R – Retardation of growth
- D – Deafness (sensorineural hearing loss)

We offer *PTPN11* sequencing (exons 7, 12, and 13) and *RAF1* sequencing (exons 1-17) for the diagnosis of LEOPARD syndrome.

**Cardio-Facio-Cutaneous (CFC) Syndrome** is characterized by features similar to those seen in individuals with NS:

- Characteristic facial features
- Congenital heart defects
- Skin and hair abnormalities
- Mild to severe mental retardation
- Postnatal growth deficiency

Mutations in *BRAF* have been detected in 78% of individuals with a clinical diagnosis of CFC. *KRAS* mutations have been detected in 7% of individuals with CFC, and *MEK1* and *MEK2* mutations in 13% of individuals with CFC. The LMM offers genetic testing for all four of these genes.

**Costello Syndrome** is similar to NS and CFC and is characterized by:

- Characteristic craniofacial features
- Skin findings: deep palmar and plantar creases, hyperpigmentation and nasal papillomas
- Failure to thrive and developmental delay
- Cardiac anomalies
- Skeletal problems
- Predisposition to malignancy

Mutations in *HRAS* (with majority of mutations in exon 2) have been reported in 87% of patients with CS. Sequencing of *HRAS* is available at the LMM.