

# Noonan Syndrome: What Physicians Need to Know CME

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## Target Audience

This activity is intended for endocrinologists, pediatricians, and other physicians interested in the diagnosis and treatment of Noonan syndrome.

## Goal

The goal of this activity is to facilitate the recognition and management of individuals with Noonan syndrome.

## Learning Objectives

Upon completion of this activity, participants should be able to:

1. Review the incidence and genetic components of Noonan syndrome.
2. Identify the phenotypic features and morbidities that may be associated with Noonan syndrome.
3. List screening evaluations, specific assessments or referrals that should be included in the routine management of a child with NS.
4. Describe the effects of treatment with growth hormone in a patient with Noonan syndrome.

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## Contents of This CME Activity

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Noonan Syndrome: What Physicians Need to Know

### Overview

Noonan syndrome is one of the most common nonchromosomal syndromes seen in children with congenital heart disease. Although almost all types of cardiac abnormalities have been associated with a diagnosis of Noonan syndrome, the most common abnormality is pulmonary stenosis.

Affected individuals have characteristic facial features, are usually short in stature, and often have a chest deformity. The syndrome can not only be inherited as an autosomal dominant disorder with variable expression, but also is frequently sporadic.

In 1962, a clinical study of associated noncardiac malformations in children with congenital heart disease identified 9 (6 males and 3 females) with a phenotype suggestive of Turner syndrome (TS); all had valvular pulmonary stenosis.<sup>[1]</sup> The investigator believed these findings provided evidence of a previously unidentified syndrome.

Dr. John Opitz maintained that the eponym Noonan syndrome was appropriate, based on Noonan's recognition that malformations occurred in both males and females, could be found in children with normal chromosomes, could be inherited, and were associated with cardiac defects. When a report describing the original 9 patients plus 10 additional ones was published in 1968,<sup>[2]</sup> the eponym Noonan syndrome (NS) was used in the medical literature for the first time.

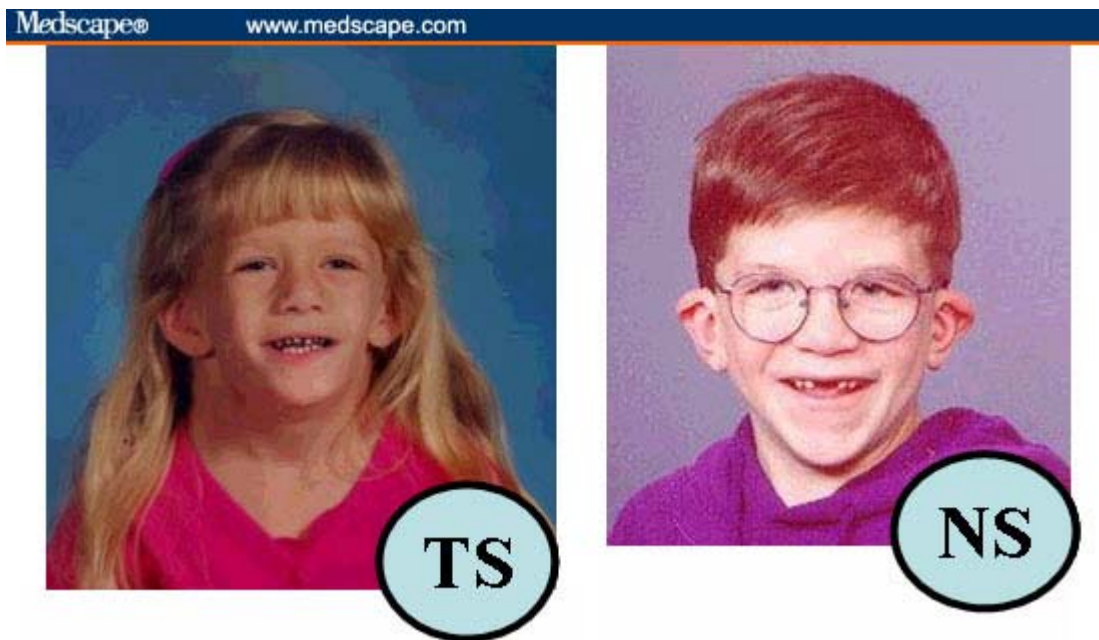
### Incidence

Although Nora and colleagues<sup>[3]</sup> estimated the frequency of NS to be 1 in 1000 to 1 in 2500 live births, no definitive incidence studies have been conducted. NS occurs worldwide, and there appears to be no racial predilection. The variability of the syndrome is very wide -- patients can appear as normal variants and remain undiagnosed; individuals with severe NS can be recognized as abnormal from early infancy.

Kramer and colleagues<sup>[4]</sup> reported that among 1016 children with a variety of congenital heart defects, 1.4% had NS. Roberts and colleagues<sup>[5]</sup> found that 7% of children requiring surgery for pulmonary stenosis had NS.

## Noonan Phenotype

It may also be difficult to distinguish NS from several other syndromes such as cardio-facio-cutaneous syndrome, Costello syndrome, LEOPARD syndrome, and neurofibromatosis in patients who have a Noonan phenotype. Previously, NS was confused with TS in females and "male Turner" syndrome in males (Figure 1). Distinctive facial features found in patients with NS include hypertelorism; epicanthal folds; downslanting, palpebral fissures; a high arched palate; low-set, posteriorly rotated ears; malar hypoplasia; ptosis; and a short neck.



**Figure 1.** Comparison of patients with Turner syndrome and NS.

Although there was early recognition of familial cases of NS, the majority of cases appear to be sporadic. A study comparing sporadic to familial cases found a significant change in phenotype seen with time<sup>[6]</sup> (Figure 2). When photographs of a parent taken at the same age as their affected child were compared, some revealed a similarity that was not initially apparent in the parent. Allanson and colleagues<sup>[6]</sup> demonstrated that "sporadic" cases became familial once the changing phenotype was recognized. These investigators urged that a photograph of each parent, taken at the same age as the affected child, be evaluated in all children diagnosed with NS. It is surprising how frequently an adult with relatively mild features is not identified until their child is diagnosed. Today, genetic testing can confirm the diagnosis.



**Figure 2.** Patient Phenotype: Infancy to Adulthood

## Genetic Basis

### Inheritance

NS is an autosomal dominant (AD) disorder with complete penetrance and variable expressivity. For every gene in the body, there are 2 copies: 1 from the mother and 1 from the father (with the exception of X and Y chromosome genes in males). An AD disorder is caused by a problem with only 1 copy of a gene and thus can be passed down from generation to generation.

Penetrance is an all-or-none phenomenon. NS is a completely penetrant disorder; every generation has some manifestations. However, these manifestations could be so subtle as to go unrecognized. Expressivity refers to how severe those manifestations are. So although NS is passed down in families and those affected in each generation have some of the signs or symptoms, there is considerable intrafamilial variability in expression. There can be children with no heart disease, with mild pulmonary valve stenosis, or with severe pulmonary stenosis requiring surgical intervention within a single sibship. NS does not exhibit anticipation -- therefore, the manifestations do not worsen with each subsequent generation.

When a child has been diagnosed with NS, about half of the time it is inherited from a parent and half of the time it is sporadic -- and the child is the first in the family to have the disorder. Sporadic mutations have been associated with advanced paternal age.<sup>[7]</sup>

If a child with sporadic NS has biologic children, it can be passed to the next generation (inherited). When 1 parent has NS, each offspring will also have a 50% chance of having NS. When 2 unaffected parents have a child with NS, they have a 1% to 3% risk of having a second affected child. This risk is due to germline mosaicism, the theoretical risk that multiple egg or sperm cells harbor a NS genetic mutation.

### Molecular Genetics

It was not until the discovery of the *PTPN11* gene in 2001 that the molecular genetic causes of NS began to be uncovered. Because of similar facial features, growth issues, and skeletal findings with Turner syndrome, investigations began looking for linkage to the X chromosome, but none were found.<sup>[8]</sup>

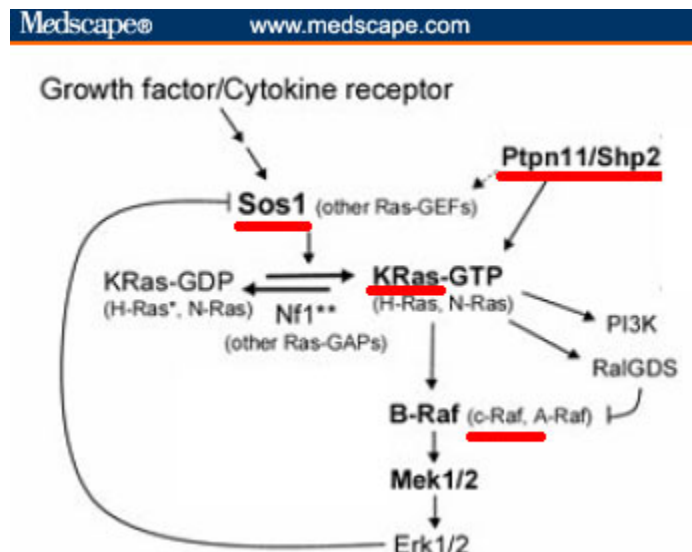
There are many cases of children who exhibited findings of both NS and neurofibromatosis type 1. It was initially hypothesized that NS could be caused by a gene close to the *NF-1* gene on chromosome 17, but this was not the case.<sup>[9,10]</sup> When linkage analysis was performed on 2 multigenerational families, a chromosomal band 12q24 locus was found.<sup>[11,12]</sup>

Chen and colleagues<sup>[13]</sup> discovered that both the Egrf (epidermal growth factor receptor) and Shp-2 (src homology region 2-domain phosphatase-2) proteins were components of a growth factor-signaling pathway required for semilunar valvulogenesis. Shp-2 is involved in intracellular signaling downstream to several growth factors, cytokine, and hormone receptors, and is encoded by the *PTPN11* -- a gene that had previously been localized to 12q24.1-24.3.<sup>[14]</sup> Because of its localization and role in cardiac valvulogenesis, *PTPN11* was considered an excellent candidate gene for NS.

The *PTPN11* protein product, SHP-2, has 2 tandemly arranged SH2 domains at the N terminus (N-SH2 and C-SH2), followed by a protein phosphatase domain.<sup>[15]</sup> SHP-2 acts in an active or inactive conformation regulated by the N-SH2 domain. Examination of 22 unrelated NS patients revealed that about half had a *PTPN11* gain of function missense mutation and these mutations were located in and around the N-SH2 interactive surfaces.<sup>[16]</sup> The first NS gene had been discovered.

Genotype phenotype analysis showed that those with a *PTPN11* mutation are more likely to have pulmonary valve stenosis<sup>[17]</sup> and atrial septal defect<sup>[18]</sup> and those without are more likely to have hypertrophic cardiomyopathy (HCM).<sup>[17]</sup> Otherwise, the 2 groups are remarkably similar. Because the groups are so alike, this implied that the genes causing the remaining cases of NS must be close by in the pathway SHP-2, a component of the RAS MAP kinase signaling pathway.

Since 2001, 3 additional genes have been found to cause NS -- *KRAS*, *SOS1*, and *RAF* -- all components of this pathway and all mutations that lead to increased RAS signaling (Figure 3).



**Figure 3.** The Ras MAP kinase pathway. (Adapted from reference 19.)

Causative NS genes are all important regulators of this pathway. Pathogenic mutations are gain-of-function and lead to increased Ras signaling.

*KRAS* gain of function missense mutations have been found in a total of 18 cases, representing approximately 1%-3% of all NS cases.<sup>[20-22]</sup> *KRAS* is a small G protein activated by the exchange of bound guanosine diphosphate (GDP) for guanosine triphosphate (GTP) and possesses self-inactivating GTPase activity thought to be reduced by the NS mutations.<sup>[18,19]</sup> Children with *KRAS* mutations are reported to have more severe cognitive and developmental delays than children with NS without a *KRAS* mutation.<sup>[20,21]</sup>



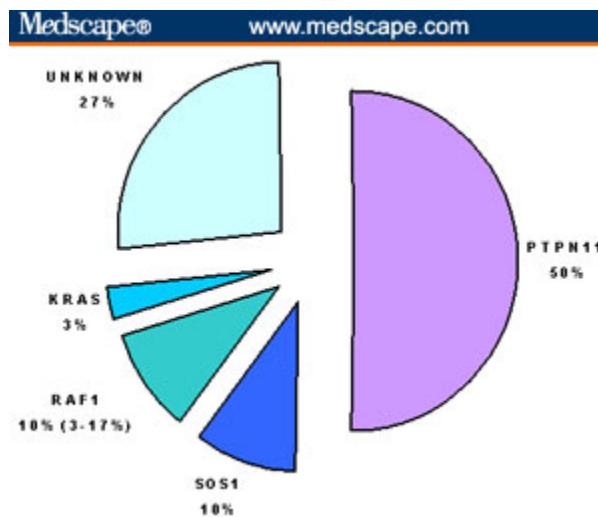
Mutations in another member of the Ras Map kinase pathway, *SOS1*, have recently been shown to cause about 10% of NS.<sup>[19,23]</sup> Like the SHP-2 protein, the *SOS1* protein exists in both an active and inactive conformation. In the active conformation, there are 2 RAS binding sites. In the inactive conformation, the N terminal domain blocks these binding sites and the protein is autoinhibited.<sup>[24,25]</sup> The NS associated *SOS1* missense mutations are thought to disrupt the orientation of the N terminus, exposing the RAS binding sites, and leading to constitutive activation.<sup>[19,23]</sup> Children with NS caused by an *SOS1* mutation are thought to be less likely to have short stature and cognitive delays and more likely to have ectodermal abnormalities such as curly hair and facial keratosis pilaris.<sup>[23]</sup>

Finally, recently published data showed that gain-of-function *RAF1* mutations also cause NS.<sup>[26,27]</sup> *RAF1* protein contains 3 domains: CR1 and CR2, thought to be negative regulators of the protein, and CR3, the kinase domain.<sup>[28]</sup> Serine and threonine phosphorylation regulate whether *RAF1* is in the active or inactive state.<sup>[29]</sup> There is a much higher prevalence of hypertrophic cardiomyopathy (HCM) in those with a *RAF1* mutation (80%) than in those with Noonan syndrome in general (18%),<sup>[30]</sup> particularly in those with a CR2 domain mutation.<sup>[26,27]</sup>

It is unclear what percentage of NS cases are caused by *RAF1* mutations, as the 2 initial publications reported respective findings of 3%<sup>[26]</sup> and 17%.<sup>[27]</sup> Because of the close correlation of HCM with the presence of a *RAF1* mutation, the prevalence will be related to the incidence of HCM in the NS cohort being studied.

## Genetic Testing

One third of cases of NS are not explained by a *PTPN11*, *KRAS*, *SOS1*, or *RAF1* mutation. This remains an active area of research. In choosing the order in which to complete genetic testing for a child with NS, there are 2 considerations. The first is the mutation detection rate for each gene, and the second is the phenotypic differences associated with each gene (Figure 4).



**Figure 4.** Molecular genetic causes of Noonan syndrome.

As the majority of mutations are found in the *PTPN11* gene, this is the logical place to start. Genotype phenotype relationships can then guide the next step.

A child without a *PTPN11* mutation who has HCM could next have *RAF1* testing. A child with normal stature, minimal or no developmental delays, and facial keratosis pilaris without a *PTPN11* mutation could next have *SOS1* testing. A child without a *PTPN11* mutation with

significant developmental and cognitive delays could next have *KRAS* testing. However, because none of these features is caused exclusively by 1 gene (eg, HCM has been reported in *PTPN11*, *SOS1*, and *RAF1* associated with NS), it is also reasonable to test all 4 genes in a sequential fashion, based purely on the likelihood of finding a mutation (*PTPN11* > *SOS1* > *RAF1* > *KRAS*). Normal gene sequencing does not eliminate, but does decrease, the possibility that the child has NS. Thirty percent of children with NS will have normal test results. A summary of NS genes and associated physical findings is provided in Table 1.

**Table 1. Mutation Detection Rate and Differentiating Genotype Phenotype Correlations in Noonan Syndrome**

Noonan Syndrome Gene	Percentage of all NS Cases	Differentiating Feature(s)
<i>PTPN11</i>	50%	Higher prevalence of pulmonary stenosis and atrial septal defect
<i>RAF1</i>	3%-17%	Approx. 80% of cases have hypertrophic cardiomyopathy
<i>SOS1</i>	10%	More cutaneous findings, less short stature, less cognitive delay
<i>KRAS</i>	1%-3%	More severe cognitive and developmental delays

## Natural History and Associated Morbidities

### Prenatal Course

A prenatal diagnosis of NS is usually not feasible. However, maternal polyhydramnios is common. Ultrasound findings suggestive of NS in utero include cystic hygroma that may develop late in the first trimester and regresses or disappears late in the second trimester;<sup>[31]</sup> hydrops will develop occasionally.<sup>[32]</sup> Although suggestive, none of these findings are specific for NS. However, if a suspected gene is found, prenatal diagnosis can be confirmed by DNA study of amniotic cells.

### Birth and Early Infancy

The majority of newborns with NS are not recognized as being abnormal at birth. Height and weight are usually within normal range. Overt edema is not usual. Many infants with NS lose a substantial amount of weight during the first week of life, suggesting fluid retention.

Although many infants with NS do quite well immediately following birth, most will show an early decrease in height velocity. Feeding problems are also frequent in early infancy, consisting primarily of poor appetite and vomiting. Sharland and colleagues<sup>[9]</sup> reported that although approximately 33% of infants with NS had no or mild feeding difficulties, 33% had moderate problems and about 25% had feeding problems severe enough to require tube feedings.



Many young infants with NS are hospitalized due to lethargy, poor feeding, or vomiting and subsequently evaluated for possible sepsis or failure to thrive. NS should be suspected in any infant that appears dysmorphic, has some hypotonia, poor feeding, and failure to thrive. Fortunately, if feeding problems are present in children with NS, these resolve later in infancy.

## Development

In general, patients with NS demonstrate mild motor delay. This may be partly attributed to muscular hypotonia -- a finding that is quite prominent in some patients. Sitting is often delayed until about 10 months of age, and walking occurs closer to 2 years. Talking is also delayed to about 2.5 years.

Mental retardation is not common and if present, is usually mild. However, learning disabilities are frequent. Some learning disabilities may be attributed to eye problems or hearing impairment. All children with NS should have both an eye examination and hearing evaluation before beginning schooling.

In general, the average intelligence quotient (IQ) of a child with NS will be about 10 points lower than what is seen in normal children. However, many have normal IQs and graduation from college and achievement of PhD degrees has been observed.

There is limited information available from psychological studies of children with NS. Some investigations have shown visual-constructural problems and verbal performance discrepancies.<sup>[33,34]</sup>

Speech problems are frequent. Additionally, it is not uncommon for children to develop behavioral problems such as attention deficit disorder, hyperactivity, and eating problems.

## Growth

Weight and height are usually in the normal range at birth, but short stature develops in about 80% of children with NS. In general, a 2-year delay between bone age and chronologic age is present. As a result, height may continue to increase until individuals reach their early 20s. Therefore, approximately one third of males and approximately one third of females attain a height within normal range in adulthood. However, more than 1/2 of females and one third of the males remain below the third percentile of height as adults.<sup>[35]</sup> The reason that more females than males are short as adults is because they typically have a normal puberty, whereas puberty is delayed in males.<sup>[36]</sup>

The etiology of short stature has not been entirely elucidated. Partial skeletal dysplasia may be involved, as they are found to have disproportionably larger trunk than legs, similar to what is seen with Turner syndrome (Figure 5).



**Figure 5.** Trunk-to-leg ratio in patient with NS.

As in Turner syndrome, children with NS were thought not to be growth hormone (GH) deficient. However, Noordam and colleagues<sup>[37]</sup> showed that 50% of those studied had mean overnight GH concentration below the lower limit of the normal range.<sup>[37]</sup> Moreover, children with NS were found to have a high basal metabolic rate, and a wide GH pulse. GH secretion is usually normal after pharmacologic stimuli, although a subnormal response has been documented in a few patients.<sup>[37]</sup>

The majority of children with NS also have a low insulinlike growth factor-1 (IGF-I) level despite GH status; it is speculated these individuals have a failure in GH postreceptor signaling.<sup>[37-39]</sup> High GH and low IGF-I levels are particularly common in children with the *PTPN11* gene mutation<sup>[40,41]</sup>; they may respond less well to GH treatment. Although those with Turner syndrome have been shown to have increased levels of other less active GH isoforms,<sup>[42]</sup> this does not seem to be the case in children with NS (Osio D, personal communication, 2007).

## Eye Findings

All children with NS should undergo an eye examination. The Noonan phenotype includes hypertelorism, ptosis, epicanthal fold, as well as an antimongoloid slant to the eyes. Most

importantly, refractive errors are very common, as are strabismus and amblyopia.<sup>[43]</sup> An occasional patient has been reported to have coloboma. It is of interest that very light blue or light green irises are also frequently seen in children with NS when unaffected family members have a much darker eye color.

## **Orthopaedic Findings**

More than 90% of patients with NS have a chest deformity such as pectus carinatum or pectus excavatum. Scoliosis or kyphosis occurs in 10% to 15%, talipes equinovarus is found in about 10% to 15%, and a small percentage has radial-ulnar synostosis. The chest is often shieldlike and nipples appear widely spaced.

Joints are often hyperextensible and muscle hypotonia is common -- this often leads to flat feet. Often, there is also an increased carrying angle at the elbows. Leg aching at night is a frequent complaint.

## **Genitourinary Findings**

A delay in puberty corresponding to the delay in bone age is commonly seen in both males and females. Females often experience a delay in menses, but normal sexual development is usual. Undescended testicle (1 or both testes) is present in more than 50% of males.

Females appear to have normal fertility. Among males with undescended testes there is sometimes a decrease in fertility, but the majority is still able to reproduce. Renal anomalies are present in about 10%, but are generally of little clinical consequence.

## **Neurologic Findings**

Seizures are occasionally reported, but are not frequent and are usually easily controlled.<sup>[44]</sup> Unexplained peripheral neuropathy has been seen, but is uncommon. Occasionally, patients with NS have hydrocephalus. Although myelomeningocele can occur, it is usually mild.

Of interest is an increased incidence of symptomatic Arnold-Chiari malformation in individuals with NS. Poor coordination may be present and can be attributed to a combination of hypotonia and visual problems.

## **Skin and Hair Findings**

Prominent fetal pads on the fingers and toes are common. Curly hair is often a feature, but the occasional patient will have both sparse hair and eyebrows. Nevi, freckles, and café-au-lait spots are all frequently observed.

There is a tendency to form extensive keloids following a surgical procedure. One patient with a tethered cord required multiple surgical procedures due to recurrent tethering caused by excessive scarring. Recurrence developed after surgery in several patients with Arnold-Chiari malformation because of excessive scar tissue formation.

## **Dental Findings**

Malocclusion is relatively common. Cherubism, a condition in which there is swelling of the mandible attributed to multiple giant cell lesions, is uncommon.<sup>[45]</sup>

## Hematologic Findings

Unexplained hepatosplenomegaly is usually present in about 20% of patients and most often occurs in infancy. Easy bruising is fairly common. A variety of bleeding problems have been described. Partial deficiency of factor XI was the first to be identified<sup>[46]</sup>; deficiencies in factors VIII and XII, thrombocytopenia, and platelet dysfunction defects have subsequently been noted.<sup>[47]</sup>

Severe bleeding is not common, but life-threatening bleeding in an infant with NS was recently reported.<sup>[48]</sup> Bleeding did not resolve with the use of fresh-frozen plasma and platelet transfusions. Fortunately, the infant was successfully treated with recombinant factor VIIa.

If there is any suspicion of a bleeding problem, a prothrombin time, a partial thromboplastin time, bleeding time, and platelet count should be obtained. Use of aspirin or of aspirin-containing products should be avoided in all children with NS.

Young children, especially those with 218C>T mutation in the PTPN11 gene, are at an increased risk for juvenile myelomonocytic leukemia (JMML).<sup>[49]</sup> When this occurs in children with NS, the course is more benign than when the condition occurs in otherwise normal children. Except for the known increased risk for JMML, it is not clear whether individuals with NS are at increased risk for malignancy. Other malignancies reported include acute lymphoblastic leukemia, neuroblastoma, schwannoma, and testicular and breast cancer.

## Lymphatic Findings

Lymphatic abnormalities occur in < 20% of children with NS, but may cause serious problems. Fetuses with cystic hygroma that tends to regress by the third trimester have been identified. Puffy hands and feet are relatively common findings in severely affected newborns. This edema generally subsides, but lymphedema may develop later in childhood or in adulthood. Intestinal lymphangiectasia with protein-losing enteropathy,<sup>[50]</sup> pulmonary lymphangiectasia,<sup>[51]</sup> and spontaneous chylothorax have been seen; chylous effusions are a risk following heart surgery.

Although reports of lymphangiography have been limited, findings have demonstrated hypoplasia or absence of superficial lymphatic channels.<sup>[52]</sup> Complications of these abnormal lymphatic vessels can result in chylothorax, chyloperitoneum, lymphopenia, or malnutrition. Persistent chylothorax, particularly in young infants, may be very difficult to treat and is one of the most common causes of death in this age group.

## Cardiovascular Findings

The majority of patients with NS have some type of cardiac abnormality. In patients undergoing cardiac ultrasound, an abnormality was found in over 80%.<sup>[53]</sup> As previously noted, the most characteristic lesion is pulmonary stenosis, often associated with a dysplastic pulmonary valve.

When the pulmonary valve is only mildly dysplastic and there is no significant obstruction, long-term prognosis is usually excellent. However, progressively severe pulmonary stenosis develops in some patients during childhood. Unfortunately, if the valve is dysplastic, balloon valvuloplasty may not successfully alleviate the gradient.

Those with severe obstruction usually require surgical treatment. A simple valvotomy may not adequately relieve the obstruction. It is often necessary to excise the entire valve and sometimes resection of anomalous muscle bundles in an outflow track patch is required. Primary pulmonary hypertension has been documented in several patients; lung transplantation has been successfully performed in 1.

In addition to pulmonary stenosis, there is a high association of atrial septal defects and pulmonary artery branch stenoses. Ostium primum atrial defects, ventricular septal defects, tetralogy of Fallot, Epstein malformation, and anomalous pulmonary venous return have also been reported in children with NS.

Although right sided lesions predominate, valvular aortic stenosis, subaortic stenosis, supra-aortic stenosis, coarctation of the aorta, and patent ductus arteriosus has also been diagnosed. To date, there has not been any report of transposition of the great arteries.

The cardiac valves may also be dysplastic. Mitral valve prolapse, either isolated or associated with additional cardiac lesions, is common. Coronary artery anomalies including coronary fistula, right coronary artery aneurysm, and single artery and proximal left coronary artery occlusion have been documented.

Some degree of HCM is believed to occur in 20% of individuals with NS. It is of interest that those with the PTPN11 gene have a low incidence; those with a Noonan variant called LEOPARD syndrome have a high incidence.<sup>[53]</sup>

HCM may be present in infancy or develop later in life, and gradually increase or remain stable for many years. In infants, HCM can rapidly progress and is associated with significant mortality. Treatment of older children is similar to that of nonsyndromic children.

## **Screening/Routine Management of a Child With Noonan Syndrome**

Labeling a child as having NS should not be made without careful thought and evaluation. Early referral to a geneticist is essential. The word syndrome is frightening to some parents and suggests being abnormal, different, or imperfect. It is preferable to characterize children with NS as special -- and as having special needs.

Some children are very mildly affected and may be essentially treated as normal. Because there is such a high incidence of eye and cardiac findings, all children should have comprehensive eye and cardiac evaluations. Additionally, hearing testing should be performed. A careful developmental assessment before starting schooling is important to facilitate early diagnosis and appropriate treatment of any learning disability.

Because there may be significant delay in height, early evaluation by an endocrinologist is recommended. Treatment with GH results in a significant increase in growth velocity during the first and second year of treatment. However, the velocity and growth tends to diminish in succeeding years,<sup>[54-56]</sup> as was previously seen in all patients treated with GH. The delta height is about 1 SDS after 2 years of treatment, and no dose-dependent response is seen.<sup>[36]</sup> With GH treatment, height increase during pubertal years continues, with a substantial improvement of more than 0.5 SDS to adult height.

Several authors have claimed that the predicted adult height has been increased in patients treated with GH, but to date no randomized double-blind trials have documented the effect of long-term GH use on adult height. A comparison of historical data showed an improvement of mean height from onset of treatment to adult years of 2 SDS in males and 1.4 SDS in females.<sup>[36,57]</sup> These improvements were approximately the same magnitude as those seen with GH treatment in females with Turner syndrome<sup>[58]</sup> and short children born small for gestational age.<sup>[59]</sup>

Whether GH treatment worsens HCM in children with NS is still unresolved.<sup>[60,61]</sup> Therefore, it is recommended that GH treatment not be initiated in NS patients with serious heart failure. Cardiac function should be regularly monitored in all patients with NS treated with GH.

Similarly, children with NS being treated with GH should be regularly monitored for exacerbation or reactivation of existing malignancy,<sup>[62,63]</sup> and for decreased insulin sensitivity.<sup>[62,63]</sup> Development of lymphoma during GH treatment has been reported<sup>[36]</sup> however, studies of children with NS not treated with GH have shown an increased risk of juvenile myelomonocytic leukemia.<sup>[64,65]</sup> Transient increases in insulin levels have been observed, but no insulin resistance has been reported to date.<sup>[36]</sup>

## Long-Term Prognosis

The natural history of NS, including potential effects of increasing age on abnormal genes, is currently unknown.<sup>[66]</sup> Although children with NS may seem a bit immature because of their small size, they usually have a pleasant personality and all are truly special. The majority will grow up and function quite well in the adult world.

Individuals with NS have a 50% chance of their offspring being affected. If both parents are affected, there is 25% risk for compound heterozygosity and early fetal death is likely.

Long-term follow-up for patients with NS is essential but challenging. The transition from pediatric to adult medical care is not easy. The majority of adults have difficulty finding a physician with experience in NS; many complain that they have to educate healthcare providers about NS. Frequently, adults discontinue the regular medical follow-up they experienced as children.

The NS Support Group<sup>[67]</sup> can be an important resource for adults. Hopefully, this group will also be a resource for collection of data that could increase understanding of long term follow-up among adults with NS.

## Conclusion

All of the genes involved in NS deregulate the Ras signaling pathway, thus demonstrating that this pathway plays an important role in fetal development. It is becoming apparent that the various mutations have variable phenotypes; NS may play a role in increasing the overall understanding of developmental disorders.<sup>[68]</sup>

With the new genetic information now available, it is important for primary care physicians to become knowledgeable about NS. Timely recognition and optimal management of NS will facilitate the delivery of quality care for patients and families. Careful evaluation and genetic testing of individuals with suspected NS is important so that the phenotype of each mutation can be documented and followed.

The continued development of animal models will hopefully result in the development of therapy to prevent or improve adverse clinical effects such as short stature, hypertrophic cardiomyopathy, and learning disabilities, to name a few of the conditions associated with NS. It is also anticipated that in the near future, findings from animal models will contribute to guideline development and clinical trials of a range of therapeutic options.

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## [References](#)

[ CLOSE WINDOW ]

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