Noonan Syndrome: Clinical Features, Diagnosis, and Management Guidelines

abstract

Noonan syndrome (NS) is a common, clinically and genetically heterogeneous condition characterized by distinctive facial features, short stature, chest deformity, congenital heart disease, and other comorbidities. Gene mutations identified in individuals with the NS phenotype are involved in the Ras/MAPK (mitogen-activated protein kinase) signal transduction pathway and currently explain ~61% of NS cases. Thus, NS frequently remains a clinical diagnosis. Because of the variability in presentation and the need for multidisciplinary care, it is essential that the condition be identified and managed comprehensively. The Noonan Syndrome Support Group (NSSG) is a nonprofit organization committed to providing support, current information, and understanding to those affected by NS. The NSSG convened a conference of health care providers, all involved in various aspects of NS, to develop these guidelines for use by pediatricians in the diagnosis and management of individuals with NS and to provide updated genetic findings. *Pediatrics* 2010;126:746–759

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KEY WORDS

Noonan syndrome, *PTPN11*, *SOS1*, *BRAF*, *KRAS*, *NRAS*, *RAF1*, *SHOC2*, Ras/MAPK signal transduction, congenital heart disease, short stature

ABBREVIATIONS

NS—Noonan syndrome
CFC—cardiofaciocutaneous
MAPK—mitogen-activated protein kinase
LEOPARD—lentigines, electrocardiographic anomalies, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, and deafness
PTPN11—protein tyrosine phosphatase non–receptor type 11 gene
PVS—pulmonary valve stenosis
GH—growth hormone
ASD—atrial septal defect
HCM—hypertrophic cardiomyopathy
MPD—myeloproliferative disorder

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Noonan syndrome (NS) is a relatively common congenital genetic disorder with an estimated prevalence of 1 in 1000 to 1 in 2500 live births.[1] Characteristic findings include distinctive facial features, short stature, chest deformity, and congenital heart disease. It is an autosomal dominant disorder with complete penetrance but variable expressivity. Until recently, diagnosis was based solely on clinical findings, but genetic mutations are identifiable in ~61% of the patients. Because of the difficulty in establishing a diagnosis of NS, the Noonan Syndrome Support Group coordinated a meeting of health care providers with expertise in various aspects of the disorder with the aim of developing guidelines for its diagnosis and management. This report is the result of those efforts and is intended to provide the pediatrician with key clinical features of NS, to provide an update of currently understood genetic causes, and to present management recommendations (Table 1).

A description of the meeting methodology is provided in Supplemental Information.

HISTORY OF NS

In 1962, Jacqueline Noonan, a pediatric cardiologist, identified 9 patients whose faces were remarkably similar and who, in addition, had short stature, significant chest deformities, and pulmonary stenosis.[1] In 1968 Dr Noonan published a case series with these 9 plus an additional 10 patients.[2] The eponym "Noonan syndrome" was adopted in recognition of Dr Noonan, because she was the first to indicate that this condition occurred in both genders, was associated with normal chromosomes, included congenital heart defects, and could be familial.[3]

CLINICAL DESCRIPTION AND DIFFERENTIAL DIAGNOSIS

Facial and musculoskeletal features most often lead to the diagnosis of NS. The facial appearance is most characteristic in infancy (Fig 1) and early-to-middle childhood and becomes more subtle in adulthood[4] (Fig 1*B*). In the newborn infant with NS, the head is large with a small face tucked beneath a large cranium, a tall forehead, and narrowing at the temples. The eyes are wide-spaced and prominent with epicanthal folds, ptosis, and horizontal or down-slanting palpebral fissures (95%). There may be telecanthus as well as hypertelorism. The nose is short and broad with a depressed root and full tip. The ears are low-set, are posteriorly rotated, and have an oval shape and thickening of the helix (90%). The upper lip is distinctive with a deeply grooved philtrum with high, wide peaks to the vermillion of the upper lip (95%), and full lips. Generally, the neck is short with excess skin and a low posterior hairline (55%). In middle-to-late childhood, facial appearance often lacks expression and resembles the face of an individual with a myopathy. By adolescence, face shape is an inverted triangle, wide at the forehead and tapered to a pointed chin. Eyes are less prominent. Features are sharper. There is a narrow nasal root with a thin bridge. The neck is longer, accentuating skin webbing or prominence of the trapezius muscle. The adult face may be quite unremarkable, although the same individual may have had more obvious features as an infant. Some adults, however, have typical features including ptosis, wide-spaced eyes, low-set ears with posterior rotation and thickened helix, and broad or webbed neck. In the older adult, nasolabial folds are more prominent than one would expect for that person's age, and the skin appears transparent and thin.

Hair may be wispy in the toddler, whereas it is often curly or wooly in the older child and adolescent. Regardless of age, eyes are frequently pale blue or blue-green and much lighter in color than expected for family background.

A characteristic pectus deformity of the chest with pectus carinatum superiorly and pectus excavatum inferiorly is seen in most individuals. Also, nipples are wide-spaced and low-set, and rounded shoulders are common.[5] Scoliosis is reported in 10% to 15%.[6] Other less common spinal abnormalities include kyphosis, spina bifida, vertebral and rib abnormalities, and genu valgum. Talipes equinovarus is described in 10% to 15%, other joint contractures in 4%, radio-ulnar synostosis in 2%, and cervical spine fusion in 2%. Abnormal forearm carrying angles (cubitus valgus) are found in more than half the males (10–11°) and females (14–15°).[7] Hyperextensibility is common.[7]

Because of differences in prognosis, recurrence concerns, and treatment, accurate diagnosis is essential. There are several disorders with significant phenotypic overlap with NS, such as Turner syndrome (Table 2).[8–17] For many years, before our understanding of their underlying genetic causes, cardiofaciocutaneous (CFC) syndrome and Costello syndrome were often confused for NS, particularly in the newborn period. Therefore, it was not surprising that they, like NS, were found to be caused by mutations in genes of the Ras/MAPK (mitogen-activated protein kinase) pathway. Other disorders with significant phenotypic overlap with NS include neurofibromatosis type 1, LEOPARD (lentigines, electrocardiographic anomalies, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, and deafness) syndrome, Aarskog syndrome, fetal alcohol syndrome, mosaic trisomy 22, and Baraitser-Winter syndrome. Molecular

TABLE 1 Management Recommendations

Clinical Specialty Issue	Recommendations
Genotype/phenotype issues	Genetics consultation and follow-up
	Decision whether to perform gene testing in individuals with NS phenotype should take into consideration:
	Positive gene testing can confirm NS diagnosis
	Negative test results cannot exclude the diagnosis
	Expected frequency of mutations among patients with definite NS by sequencing the 6 genes known to date is ~60%
	If sequential molecular testing is determined to be indicated (rather than simultaneous chip based analysis):
	PTPN11 sequencing should be performed first, because this gene explains the highest number of cases
	If normal, phenotype should be used to guide the choice of the next gene to sequence
	If developmental delays are absent or mild, CFC syndrome–like skin and hair findings are present, and/or patient is of normal stature, consider *SOS1* sequencing
	If HCM is present, consider *RAF1* sequencing
	For significant developmental delays or cognitive issues, consider *KRAS* sequencing
	For sparse, thin, slow-growing hair, consider *SHOC2* sequencing
	If a variant is found, consider testing the parents to provide accurate recurrence risks
Cardiovascular issues	All individuals should undergo a cardiac evaluation by a cardiologist at the time of diagnosis, including an electrocardiogram and echocardiogram
	Those found to have cardiac problems should have regular follow-up at intervals determined by the cardiologist; cardiac care should be individualized according to the specific disorder(s) present
	Some will require treatment such as balloon valvuloplasty or surgery; long-term reevaluation of these patients after treatment is essential (specifically, after successful cardiac surgery, cardiac care should not be discontinued)
	Individuals without heart disease on their initial evaluation should have cardiac reevaluation every 5 y
	Adults should not discontinue periodic cardiac evaluations even if their evaluations in childhood or adolescence were normal; unexpected cardiac findings can occur at any point in time
Growth and endocrine issues	Children should be weighed and measured regularly by the primary care provider, and the data should be plotted on appropriate growth charts (thrice yearly for the first 3 y of life and yearly thereafter)
	Children with evidence of growth failure (growth deceleration, height less than −2 SDs, or height inappropriate for genetic background) that cannot be explained by a comorbidity should be monitored more often, have nutrition optimized, have baseline laboratory tests run, and/or be referred to a pediatric endocrinologist
	Thyroid-function tests and antibodies should be obtained from any child with a goiter and/or symptoms of hypothyroidism (fatigue, constipation, poor growth, etc)
	Children with evidence of delayed puberty (no breast development in girls by the age of 13 y, no testicular enlargement in boys by 14 y of age) should be referred to a pediatric endocrinologist
	Therapeutic interventions as indicated (GH for growth failure, thyroid hormone replacement for hypothyroidism, estrogen or testosterone for pubertal delay)
Renal and genitourinary issues	All individuals should have a kidney ultrasound at the time of diagnosis; a repeat test may be needed depending on initial findings
	Individuals may be at increased risk of urinary tract infections if a structural abnormality is present
	Antibiotic prophylaxis may be considered for hydronephrosis and/or recurrent urinary tract infection
	Orchiopexy should be performed by the age of 1 y if testicles remain undescended at that time
Gastrointestinal issues	Pediatric gastroenterology/nutrition consultation for feeding difficulties/recurrent vomiting
	Further testing as indicated (upper-gastrointestinal series, upper endoscopy, pH studies, etc)
	Therapeutic interventions as indicated (antireflux medications, feeding therapy, feeding tube, surgical consult if malrotation suspected, etc)
Hematology issues	Screening CBC with differential and prothrombin time/activated partial thromboplastin time at diagnosis and after 6–12 mo of age if initial screen performed in infancy
	Bleeding symptoms
	First tier: CBC with differential count and prothrombin time/activated partial thromboplastin time
	Second tier (in consultation with hematologist): specific factor activity (factor XI, factor XII, factor IX, factor VIII, von Willebrand factor) and platelet function (bleeding time or platelet aggregation)
	Surgery: preoperative evaluation (first- and second-tier testing) of bleeding risk; hematology consultation as needed for management of bleeding risk
	Splenomegaly: CBC with differential count
	Hepatosplenomegaly: CBC with differential count, liver-function tests
	Avoidance of aspirin and aspirin-containing medications
Neurological, cognitive, and behavioral issues	Developmental screening annually
	Complete neuropsychological testing if screening result is abnormal
	Evaluations for speech pathology, PT, and OT if delays in speech, gross motor, and fine motor skills, respectively
	Early-intervention programs beginning in infancy if delays noted
	Speech therapy for speech and articulation issues, PT and OT for gross and fine motor delays
	Regular, detailed developmental evaluations throughout childhood
	Individualized education plan for school-aged children
	Electroencephalography and referral to neurology if seizures suspected
	Brain and upper-spine MRI with any neurologic problem (headaches, weakness, numbness, poor balance, etc), cranial size aberration
	Magnetic resonance angiography (after MRI) if focal/sudden neurologic signs

TABLE 1 Continued

Clinical Specialty Issue	Recommendations
Eye and ear issues	Detailed eye examination in infancy and/or at diagnosis
	Eye reevaluations as indicated if problems found or at least every 2 y thereafter
	Hearing test in infancy and/or at diagnosis with annual hearing test throughout early childhood
	Attentive management of ear infections to minimize hearing loss
Orthopedic and dental issues	Annual examination of chest and back, radiography if abnormal
	Careful oral exam at each visit
	Dental referral between the ages of 1 and 2 y and yearly visits thereafter
	Dental radiography as indicated
Lymphatic issues	Referral of those with peripheral lymphedema to specialty lymphedema clinics
	For more information, contact the National Lymphedema Network (www.lymphnet.org)
Anesthesia risk	Individuals with NS should be considered at standard risk for malignant hyperthermia when receiving general anesthesia
	Avoidance of anesthetics associated with malignant hyperthermia in those individuals with NS-like phenotype, a skeletal myopathy, and normal to modestly elevated creatine phosphokinase level and HCM
	Skeletal muscle biopsy should be considered to look for excess muscle spindles (suspect diagnosis of congenital myopathy with excess muscle spindles) in those with NS-like phenotype, a skeletal myopathy, and normal to modestly elevated creatine phosphokinase level and HCM

CBC indicates complete blood count; PT, physical therapy; OT, occupational therapy.

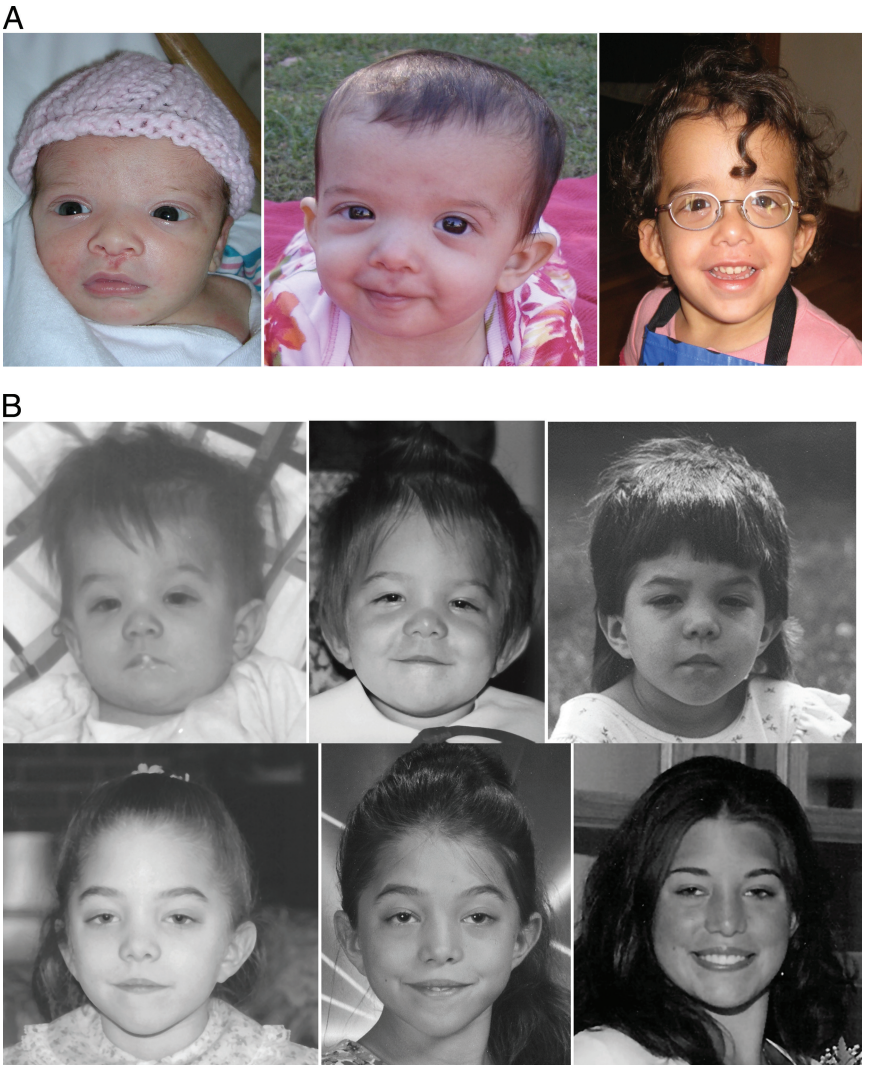

FIGURE 1
A, Patient with NS at (from left to right) 10 days, 6 months, and 2 years of age. *B*, Patient with NS at (from left to right) 4 months and 1, 2, 5, 9, and 21 years of age.

genetic testing will aid in the differentiation of NS from CFC syndrome, Costello syndrome, LEOPARD syndrome, neurofibromatosis type 1, or Aarskog syndrome. A karyotype will differentiate Turner syndrome from mosaic trisomy 22.

A discussion of scoring systems as algorithms of diagnostic criteria is provided in Supplemental Information.[7,18,19]

HISTORY OF MOLECULAR GENETIC TESTING AND GENETIC RESEARCH

In 1994, linkage analysis of a large family inheriting NS established definitive linkage to the first NS locus, defined as chromosomal bands 12q22-qter and named *NS1*.[19,20] Genetic heterogeneity was subsequently established.

In 2001, Tartaglia and co-workers[21] identified missense mutations in the protein tyrosine phosphatase non–receptor type 11 gene (*PTPN11*) as the first molecular causes of NS. This discovery was enabled by the observations that *PTPN11* resided within the *NS1* critical region and that studies with a mouse model of *PTPN11* deficiency revealed that its protein product, SHP-2, was critical for the embryologic development of the semilunar cardiac valves.[22] Because pulmonary valve stenosis (PVS) is a prominent

TABLE 2 Differential Diagnosis: Similarities and Differences Between NS and Other Disorders

Syndrome	Similarities With NS	Differences From NS
Aarskog syndrome (faciogenital dysplasia)	Similarities in NS and Aarskog syndrome are primarily facial and skeletal (hypertelorism, down-slanting palpebral fissures, and short stature).[15]	With Aarskog syndrome, no cardiovascular malformations but shawl scrotum is present; this is an X-linked recessive disorder caused by *FGD1* gene mutations.
Baraitser-Winter syndrome	Features common to both NS and Baraitser-Winter syndrome include hypertelorism, eyelid ptosis, short neck, short stature, and cognitive delays.	With Baraitser-Winter syndrome, there can be iris coloboma, pachygyria, lissencephaly, bicuspid aortic valve stenosis, and aortic stenosis[17]
CFC syndrome	Common facial, skeletal, and cardiac features in both NS and CFC syndrome include hypertelorism with down-slanting palpebral fissures, epicanthal folds, and eyelid ptosis, depressed nasal root, short stature, relative macrocephaly, PVS, HCM, and ASDs.[9] *KRAS* or *BRAF* mutations and rarely *SOS1* or *MEK1* mutations have been seen in patients with NS and those with CFC syndrome.[10–12,138]	With CFC syndrome, coarser facial features, severe feeding problems, follicular hyperkeratosis, sparse eyebrows and eyelashes, ichthyosis, and ulerythema ophryogenes; majority have moderate retardation[13]; may be caused by *MEK1* or *MEK2* mutations[10–12]
Costello syndrome	Many features common to both Costello syndrome and NS include curly hair, wide nasal bridge, eyelid ptosis, down-slanting palpebral fissures, epicanthal folds, PVS, HCM, pectus deformity, and Chiari I malformation.	With Costello syndrome, coarse facial features, wide nasal bridge, loose skin, increased pigmentation with age, deep palmar and plantar creases, papillomata of the face or perianal region, premature aging and hair loss, multifocal atrial tachycardia, moderate mental retardation, and ulnar deviation of the wrist and fingers[14]; caused by *HRAS* mutations
Fetal alcohol syndrome	Common features to both NS and fetal alcohol syndrome include growth delay, developmental delay, hypertelorism, epicanthal folds, PVS, and ASD.	With fetal alcohol syndrome, born small for gestational age, microcephaly, cleft palate, small palpebral fissures, smooth philtrum, thin-lip vermilion, and a wider range of cardiac defects including ventricular septal defect, endocardial cushion defect, conotruncal abnormalities, and coarctation of the aorta
LEOPARD syndrome	Common features to LEOPARD syndrome and NS include hypertelorism, PVS, HCM, and short stature; caused by *PTPN11*, *RAF1*, *or BRAF* gene mutations	With LEOPARD syndrome: Sensorineural deafness, multiple skin lentigines, pigmented lesions, conduction abnormalities, 30% have mental retardation
Mosaic trisomy 22	Similar facial features include hypertelorism and ptosis.	In mosaic trisomy 22: No congenital heart defects are seen,[16] and cognitive development more impaired.
Neurofibromatosis type 1	Some people with neurofibromatosis type 1 gene mutations have NS-like facial features and PVS	With neurofibromatosis type 1, multiple café au lait, axillary, and inguinal freckling, cutaneous neurofibroma, and iris Lisch nodules
Turner syndrome	Girls with NS and Turner syndrome can have short stature, eyelid ptosis, increased internipple distance, webbed neck, and kidney malformations.[8]	Cardiac features are typically left-sided in Turner syndrome but right-sided in NS; coarctation of the aorta and/or bicuspid aortic valve are more characteristic of Turner syndrome; girls have gonadal dysgenesis in Turner syndrome; normal fertility in girls with NS. Turner syndrome is attributable to loss of 1 sex chromosome.

feature of NS, these investigators reasoned that *PTPN11* was a leading positional candidate gene in *NS1*. In addition, Tartaglia and co-workers recognized that SHP-2, a protein tyrosine phosphatase with largely positive regulatory roles in Ras/MAPK signaling, participated in signaling downstream from several ligand-receptor complexes with possible relevance to the pleiomorphic abnormalities observed in NS (eg, fibroblast growth factor for bone development, growth hormone [GH] and insulin-like growth factor for somatic growth). The reasoning of these investigators proved correct, because they observed *PTPN11* missense mutations in 2 medium-sized families inheriting NS in a pattern consistent with linkage to *NS1* and then additional mutations in approximately half of a small number of sporadic cases or small families with NS.

Subsequent molecular discovery indicated that other genetic syndromes that resembled NS phenotypically, Costello and CFC syndromes, proved not to be allelic.[23–26] LEOPARD syndrome, on the other hand, proved to be allelic with *PTPN11*; mutations account for ~90% of cases, and specific mutations, particularly Y259C and T468M, are prevalent only in LEOPARD syndrome.[27,28] Other Ras/MAPK genes were then considered as candidate genes that might be mutated in patients with NS that is not explained by *PTPN11*. *HRAS* mutations were shown to cause Costello syndrome, and 4 Ras/MAPK genes (*KRAS*, *BRAF*, *MEK1*, and *MEK2*) were mutated in CFC syn-

TABLE 3 Summary of Postnatal Mutation Testing for NS

Gene	Total No. of Subjects	No. of Studies	Mutation-Positive Patients, *n* (% of Study Cohort)	% of All Cases Genotyped	Comments
PTPN11[12,25,26,30–33,45,51–53,139]	877	13	359 (40.9)	40.9[a]	25% of mutations were Asp[308]
KRAS[16,20,30,53,54,139]	616	6	15 (2.4)	1.4	*PTPN11*-negative subjects had more broadly spread mutations
SOS1[30,49,53,59,139]	311	5	60 (19.3)	11.1	Subjects were *PTPN11*- and *KRAS*-negative
RAF1[17,30,53,140]	304	4	31 (10.2)	4.7	Subjects were *PTPN11*-, *KRAS*-, and *SOS1*-negative
BRAF[55,139,140]	334	3	6 (1.8)	0.8	Subjects were *PTPN11*-, *KRAS*-, *SOS1*-, *RAF1*-negative
SHOC2[34]	96	1	4 (4.2)	1.7	Subjects were *PTPN11*-, *KRAS*-, *SOS1*-, *RAF1*-, and *BRAF*-negative
NRAS[35]	733	1	4 (0.5)	0.2	Subjects were *PTPN11*-, *KRAS*-, *SOS1*-, *RAF1*-, and *BRAF*-negative
Total	[a]	32	[a]	61	—

Shown are results of postnatal mutation testing from studies that included ≥20 patients with the NS phenotype. All studies took a sequential genotyping approach.
[a] Total values were not calculated for columns 2 and 4 because of overlap of patients (ie, mutation-negative patients were often tested again in separate studies for subsequent mutations).

drome.[10,11,29] By using this candidate gene approach, 6 additional Ras/MAPK candidate genes were identified from 2006 to the present: *KRAS*, *NRAS*, *SOS1*, *RAF1*, *BRAF*, and *SHOC2*.[12,30–35]

Genetic Testing for NS

The currently available commercial tests use different technologies (dideoxynucleotide sequencing, denaturing high-performance liquid chromatography, and oligonucleotide-based microarray sequencing) that fundamentally are based on the presence of missense or small insertions/deletions in the coding regions and flanking intron boundaries of genes that cause NS. Although gross chromosomal abnormalities (interstitial deletions, duplications, and balanced translocations) have rarely been identified in patients with phenotypes that closely resembled (or were) NS,[36–41] routine karyotyping or copy-number analysis is not recommended at this time for typical NS cases. It may be considered for atypical cases or when there is particularly severe neurocognitive involvement.

Postnatal Mutation Testing for NS

Table 3[12,30–35,42–55] summarizes the studies that comprised ≥20 subjects of postnatal mutation testing for NS since 2001. There are important limitations in the interpretation of these data, including the heterogeneity in NS diagnostic clinical criteria, the occurrence of phenotyping at different ages, and a case-mix sensitivity (the rate of *PTPN11* mutations among familial cases of NS is nearly double that among sporadic cases[42]). Mutations in the 7 genes identified for NS to date account for 61% of postnatal cases. There is currently no information concerning the number of cases, if any, that harbor more than 1 mutation for NS because all studies took a sequential genotyping approach. Because 1 center recently introduced the use of microarray-based sequencing in which all relevant genes are analyzed in parallel, it will be of interest to discover whether multiple hits are observed in some subset of patients with NS.

A suggested algorithm for individual genotyping is shown in Table 1. The rationale for this algorithm and a discussion of prenatal mutation testing in NS is provided in Supplemental Information[56–58]).

GENOTYPE/PHENOTYPE CORRELATIONS

Among the mutated genes that account for NS, many different genotype/phenotype correlations have been made. No phenotypic features are found exclusively among 1 genotype, probably because of genetic and epigenetic factors that influence both penetrance and expressivity. Table 4 summarizes some genotype/phenotype correlations that may be useful for clinicians, but note that there are no phenotypic features exclusive to a specific genotype. There are, however, significant differences in the risk of various NS manifestations based on the causative gene.

PTPN11 mutations have been consistently associated with the presence of a pectus deformity, easy bruising, the characteristic facial appearance, and short stature.[49,50,59] Children with *SOS1*-associated NS are more likely to have CFC syndrome–like skin findings (keratosis pilaris, sparse hair, curly hair, sparse eyebrows)[53] and less likely to have short stature[53] or impaired cognitive functioning.[53,60] Patients with NS caused by missense mutations in *PTPN11* are more likely to have PVS and atrial septal defects (ASDs) and less likely to have hypertrophic cardiomyopathy (HCM) than people with NS without a *PTPN11* mutation.[21,42,49,50] Those with a pathogenic *SOS1* mutation are more likely to have PVS than those with NS who have neither an *SOS1* nor a *PTPN11* mutation.[33] It is remarkable that 80% to 95% of children with *RAF1* mutations have HCM.[31,32] Pa-

TABLE 4 Genotype/Phenotype Correlations

Gene	Most Common Cardiovascular Features	Most Common Growth Features	Most Common Developmental Features	Most Common Skin/Hair Features	Most Common Other Features
PTPN11	PVS	Overrepresentation of short stature	N308D and N308S: little or no cognitive delays	—	—
	Underrepresentation of HCM	Lower IGF-1 levels	—	—	—
KRAS	—	—	More severe cognitive delay	CFC syndrome–like skin and hair findings	—
SOS1	—	Lower prevalence of short stature	Lower prevalence of cognitive delays	CFC syndrome–like skin and hair findings	—
RAF1	Overrepresentation of HCM	—	—	—	—
SHOC2	Overrepresentation of mitral valve prolapse and septal defects	Higher prevalence GH deficiency	Distinctive hyperactive behavior	Easily pluckable, sparse, thin, slow growing hair Darkly pigmented skin eczema icthyosis	Hypernasal speech
NRAS[a]	—	—	—	—	—

Shown are the phenotypic features that have been correlated to the currently known genotypes in NS.
[a] Too few cases for genotype/phenotype correlation analysis.

tients with the *SHOC2* S2G mutation have a distinctive phenotype, initially termed Noonan-like syndrome, with loose anagen hair.[61] In addition to the hair findings, the phenotype may include mitral valve and cardiac septal defects, GH deficiency, ectodermal abnormalities with darkly pigmented ichthyotic skin, hypernasal voice, and developmental issues with hyperactivity.[34]

In a study of 45 patients with NS, both bleeding diathesis and juvenile myelomonocytic leukemia were found exclusively in patients with specific *PTPN11* mutations.[49] Familial cases of NS are more likely than sporadic cases to be caused by a *PTPN11* mutation.[42] NS attributable to *KRAS* mutations seems to confer a more severe phenotype with more significant learning issues and developmental delays.[50]

CARDIOVASCULAR ISSUES

More than 80% of patients with NS have an abnormality of the cardiovascular system.[7,62–64] PVS is the most common. The valve may be dysplastic in 25% to 35% of those with PVS[64–66] and is often associated with an ASD. Isolated ASDs and partial atrioventricular canal defects are also relatively common. A broad spectrum of cardiac abnormalities has been reported, as noted in Table 5. Approximately 50% of patients with NS have an unusual electrocardiographic pattern characterized by left-axis deviation, an abnormal R/S ratio over the left precordial leads, and an abnormal Q wave.[67] Many patients have mild PVS that requires only periodic reevaluation. If the PVS is or becomes clinically significant, initial treatment is usually pulmonary balloon valvuloplasty, but it may be unsuccessful if the valve is dysplastic. With severe dysplasia, a pulmonary valvectomy or pulmonary homograft may be needed in childhood. The other cardiac defects can be treated in the standard ways.

HCM is present in ~20% of patients with NS overall but is particularly frequent with *RAF1* mutations,[31,32] and it is variable in severity and natural history. In some infants with HCM the condition resolves, whereas in others it becomes rapidly progressive and may have a fatal outcome. Others develop HCM after infancy. The course may be stable or progressive, or it may improve. Management is similar to that for any patient with HCM and may include the use of β-blocker medications or surgical myomectomy to reduce outflow obstruction.[62]

It is important for adults with NS to have lifetime cardiac follow-up. Left-sided obstructive lesions may develop in adulthood.[68] Pulmonary valve insufficiency and right ventricular dysfunction are potential problems after earlier pulmonary valve surgery. Cardiac arrhythmias have been rare in the limited reports available about long-term follow-up of adults.[6,69]

TABLE 5 Cardiac Conditions in NS

Frequent	Occasional	Rare
PVS	Aortic valvular stenosis	Pulmonary hypertension
Secundum ASD	Supravalvular pulmonary stenosis	Aortic root dilation
HCM	Bicuspid aortic valve	Aortic dissection
Partial atrioventricular canal defect	Patent ductus arteriosus	Restrictive cardiomyopathy
	Branch pulmonary artery stenosis	Dilated cardiomyopathy
	Mitral valve anomalies	Ebstein's anomaly of tricuspid valve
	Ventricular septal defect	Pulmonary atresia
	Tetralogy of Fallot	Coronary artery abnormalities
	Coarctation of aorta	

GROWTH AND ENDOCRINE ISSUES

Growth

Approximately 50% to 70% of individuals with NS have short stature.[7,70,71] Although short stature is a main characteristic of this condition, some individuals will have normal growth and stature. Birth weight and length are typically normal, but there is a sub-

sequent deceleration of height and weight to the third centile or less. The mean delay of bone age is ~2 years.[7,72] NS-specific growth charts have been published.[72,73]

Mean adult heights of European individuals with NS have been reported for women as ~153.0 cm and for men as 162.5 and 169.8 cm.[6,72] The mean adult height of North American individuals is less than the third centile in 54.5% of women (<151 cm) and 38% of men (<163.2 cm).[74,75] A higher prevalence of short stature has been found in *PTPN11* mutation-positive subjects than in mutation-negative subjects, and a lower prevalence of short stature has been described for those with *SOS1*-associated NS.[50,51]

Reports of GH-secretory dynamics have been inconsistent and are likely a reflection of the genotypic heterogeneity of NS. There have been reports of GH deficiency (45% [$n = 150$][96] 37% [$n = 27$][77]), neurosecretory dysfunction,[78–80] and completely normal GH secretion.[81,82] Insulin-like growth factor 1 levels are frequently low and were significantly lower in the *PTPN11* mutation-positive than mutation-negative patients.[81–83]

Until recently, most experience with GH in NS has been reported in studies that involved small numbers of patients with varied enrollment ages, treatment durations, doses, and responses. These studies resulted in improved growth velocity without significant adverse effects.[78–80,84–86] Although most studies have excluded patients with HCM, left ventricular wall thickness remained normal when prospectively measured in patients with NS on GH.[76–78] In addition, among the combined 889 patients from 6 articles that reported adult-height outcomes in patients with NS on GH,[84,88–92] there were only 5 reported cardiac events (2 mild progressions of PVS, 1 HCM, 1 increased biventricular hypertrophy, and 1 cardiac decompensation).

The efficacy of GH in NS can be assessed by considering adult-height data (Table 6).[84,88–91] Although different parameters were reported in these studies (ie, median versus mean values, height SD scores based on population standards versus the NS-specific standards, varied doses, etc), it seems that improved outcomes (Δ height SD score: 1.3–1.7; mean height gain: 9.5–13 cm for boys and 9.0–9.8 cm for girls[89,90,92]) occur with earlier initiation and longer duration of GH therapy, as has been demonstrated for other conditions such as Turner syndrome.[93,94]

Initial short-term data have suggested that *PTPN11*-positive patients responded "less efficiently" to GH than did the *PTPN11*-negative patients.[48] In contrast, longer-term data from comparisons of adult heights for those treated with GH among those who were *PTPN11* mutation-positive with those who were mutation-negative revealed no difference in outcome.[90] Additional studies may clarify the role of the different RAS/MAPK pathway aberrations in growth and GH responsiveness.

Other Endocrine and Autoimmune Issues

Puberty is typically, but not universally, delayed for both boys and girls with NS and is characterized by a diminished pubertal growth spurt.[72] The mean age of pubertal onset is 13.5 to 14.5 years in boys and 13 to 14 years in girls. Puberty may progress with a rapid tempo (<2 years).[92] Pubertal induction may be instituted (with careful consideration of timing for optimal height potential) for no secondary sexual characteristics in boys at 14 years (testosterone induction) and girls at 13 years (estrogen induction).

Thyroid antibodies are commonly found, but hypothyroidism is likely no more common in those with NS than in the general population.[7,95–97] There have been case reports of the occurrence of other autoimmune conditions, such as systemic lupus erythematosus and celiac disease, but their frequency is unknown.[98–100]

TABLE 6 Baseline and Treatment Growth Data From Studies That Reported Adult-Height Outcomes in Individuals With NS Treated With GH

Reference	Patients, *n* (*n* Female)	Baseline Age, y	Baseline SDS[a]	GH Dose, mg/kg per wk	Duration Therapy, y	Delta Height SDS	Height Gain
88	4 (4)	13.5	(−0.6)	0.19 for 1 y, then 0.31	3.5	(0.48)	NA
84	10 (4)	12	−3.1 (−0.7)	0.30	5.3		3.1 cm
89	18 (11)	8.6 (boys), 7.7 (girls)	−2.9 (−0.3)	0.23 ($n = 10$), 0.46 ($n = 15$) for 2 y, then dose titration[b]	7.5	1.7	13 cm (boys), 9.8 cm (girls)
91	24 (NA)	10.2 (median)	−3.24 (median)	0.24 (median [range: 0.17–0.77])	7.59 (median)	0.61 (0.97)	NA
90	29 (8)	11	−2.8 (0.0)	0.35	6.4 (median)	1.3 (1.3)	9.5 cm (boys), 9.0 cm (girls)
92	65 (30)	11.6	−3.5	0.33	5.6	1.4	10.9 cm (boys) 9.2 cm (girls)

Results are mean values unless specified otherwise. SDS indicates SD score; NA, not applicable.

[a] Height SDS is reported according to population standards and/or (NS standards).

[b] Estimated mean: 0.35 mg/kg per week.

RENAL AND GENITOURINARY ISSUES

Renal anomalies occur in 10% to 11% of those with NS and are usually of little significance.[7,98,99] Solitary kidney, renal pelvis dilation, and duplicated collecting system have been reported. Cryptorchidism occurs in up to 80% of boys, and surgical orchiopexy is required. Recent evidence suggests sertoli cell dysfunction[101] rather than cryptorchidism as the etiology of male gonadal dysfunction. Fertility does not seem to be affected in women.

HEMATOLOGY AND ONCOLOGY ISSUES

Disordered bleeding has been reported for 30% to 65% of individuals with NS.[7,102] Although the symptoms are often mild, such as excessive bruising, epistaxis, or menorrhagia, bleeding with surgical procedures can be significant. A number of coagulation-factor deficiencies (isolated and combined), thrombocytopenia, and platelet dysfunction have been described. Elevation of the activated partial thromboplastin time is frequent. Approximately 25% of individuals with NS have partial factor XI deficiency.[102–107] The bleeding symptoms do not correlate well with the degree of deficiency. A number of other coagulation factors can be depressed, and low factor XII and factor VIII activity are the next most frequent depressions.[105–107] It is important to note that although factor XII deficiency can prolong the activated partial thromboplastin time, it does not result in clinical bleeding. Low factor VIII levels can be seen with von Willebrand disease, which is a common bleeding disorder in the general population; although both low factor VIII and von Willebrand factor have been reported in NS, an accurate estimate of the prevalence of von Willebrand disease in patients with NS has not yet been determined.[105–107] Less commonly, factor IX and factor II have also been reported to be deficient in patients with NS and can contribute to bleeding risk.[105,108]

Both thrombocytopenia and platelet dysfunction have been described in patients with NS. The etiology of the thrombocytopenia is probably multifactorial and can be associated with a defect in platelet production caused by a decrease in megakaryocytes.[108] Splenomegaly may also cause mild-to-moderate thrombocytopenia and is found by ultrasound in up to 52% of patients with NS.[109] Splenomegaly may be isolated or associated with hepatomegaly. In some patients, hepatosplenomegaly or splenomegaly may be caused by NS/myeloproliferative disorder (MPD).

NS/MPD is a condition seen in infants with NS that is characterized by leukocytosis with monocytosis, thrombocytopenia, and hepatosplenomegaly. Although the clinical picture of NS/MPD resembles that of juvenile myelomonocytic leukemia, infants with NS/MPD seem to have a favorable prognosis. Although some infants with NS/MPD have been reported to develop aggressive leukemia, the majority with this condition present in the first few months of life and will remain stable or improve by 1 year of age without specific therapy.[110,111]

Despite the role of somatic *PTPN11* and *KRAS* mutations in the development of malignancies, the incidence of cancer in older children and adults with NS has not been shown to be increased over that of the general population.[6,112] However, additional studies are needed to accurately assess the risk of malignancy in individuals with NS.

NEUROLOGIC, COGNITIVE, AND BEHAVIORAL ISSUES

The neurologic, cognitive, and behavioral aspects of individuals with NS are poorly understood and extremely variable. There is an increased incidence of cognitive issues and learning disabilities, an increased incidence of brain abnormalities, and a wide array of other neurologic problems. In a study of 151 subjects with NS, 76% had feeding difficulties, 94% had ocular problems, 50% had hypermobility of joints/hypotonia, 13% had recurrent seizures, 3% had hearing loss, and 3% had peripheral neuropathy.[7] There was also a general delay in the mean age of motor milestones; sitting alone occurred at 10 months, walking occurred at 21 months, and speaking 2-word sentences occurred at 31 months.[7] Another study revealed that 84% had some type of neurologic problem.[113]

Structural malformations and deformations of the central nervous system and spinal cord are found at relatively low frequency. The most common defects are Arnold-Chiari malformation type I and hydrocephalus. The mean head circumference is at the 50th percentile; however, some individuals with NS can be microcephalic or macrocephalic.[7]

Most people with NS have normal intelligence, but 10% to 40% require special education.[7,114,115] Even among those of normal intelligence, IQ has been shown to be 10 points less than unaffected family members or 1 SD below that of the general population.[114] The observed heterogeneity in cognitive abilities in syndromes of the Ras/MAPK signaling cascade including NS can be at least partially ascribed to the individual affected genes and the type of mutation.[116] For example, *SOS1* mutations[53,60,116] and specific *PTPN11* mutations[42,60,116,117] have been associated with no or mild cognitive delays.

Children with NS have a higher rate of clumsiness, poor coordination, stubbornness, and irritability.[118] Body-image problems and poor self-esteem, depression, and social inadequacy have been noted to occur in adults with

NS.[69] Limited data are available on the psychological and psychiatric characteristics of patients with NS. Psychiatric problems are rarely found, and qualitative data in a study of 112 adults[6] with NS revealed their reporting an inability to fit in but an overall good or satisfactory quality of life. In addition, the majority of adults with NS finished high school and had paying jobs.[6,69]

GASTROINTESTINAL AND FEEDING ISSUES

Most infants (75%) with NS have feeding difficulties; poor suck with prolonged feeding time (15%), very poor suck and slow feeding with recurrent vomiting (38%), and severe feeding problems that require tube-feeding for ≥2 weeks (24%) have been described.[6,7] Investigation of some children with poor feeding has revealed immaturity of gut motility and delayed gastrointestinal motor development.[119] Gastroesophageal reflux is common, and there have been a few reports of malrotation.[109,120] Typically, the period of failure to thrive is self-limited, although poor weight gain may persist for up to 18 months.

ORAL AND DENTAL ISSUES

Oral findings in patients with NS include a high arched palate (55%–100%),[37,72,121] dental malocclusion (50%–67%),[6,120–123] articulation difficulties (72%),[71] and micrognathia (33%–43%). Some individuals with NS develop mandibular cysts, which can mimic cherubism.[124,125] The pathology of these lesions in individuals with NS is characterized by multinucleated giant cells within a fibrous stroma and is indistinguishable from cherubism. These 2 conditions, however, are genetically distinct; *SH3BP2* gene mutations are found in individuals with cherubism, whereas *PTPN11*[126] and *SOS1*[127] mutations are found in patients with NS with giant cell lesions.

TABLE 7 Support Organizations for NS

Organization	Contact Information
Noonan Syndrome Support Group	Internet: www.noonansyndrome.org; telephone: 888-686-2224 or 410-374-5245; address: PO Box 145, Upperco, MD 21155
Magic Foundation	Internet: www.magicfoundation.org; telephone: 800-362-4423 or 708-383-0808; Address: 6645 W North Ave, Oak Park, IL 60302
NORD: National Organization for Rare Disorders	Internet: www.rarediseases.org; telephone: 203-744-0100; address: 55 Kenosia Ave, PO Box 1968, Danbury, CT 06813-1968
Human Growth Foundation	Internet: www.hgfound.org; telephone: 800-451-6434; address: 997 Glen Cove Ave, Suite 5, Glen Head, NY 11545
BDF Newlife	Internet: www.bdfnewlife.co.uk; telephone: 01543 468888; address: Hemlock Business Park, Hemlock Way, Cannock, Staffordshire WS11 7GF, United Kingdom

LYMPHATIC ISSUES

NS is associated with a generalized disorder of lymphatic development, which has manifestations in fetal life through adulthood.[128,129] The overall incidence of lymphatic manifestations in all age groups of those with NS is unknown, but it is estimated to be ~20%. Peripheral lymphedema, the most common lymphatic manifestation, is seen most frequently in young infants. It typically resolves in the first few years. Adolescents and adults can develop peripheral lymphedema.[130]

Other types of lymphatic involvement that have been described in patients with NS include hydrops, chylous pleural effusions, chylothorax, pulmonary lymphangiectasis, intestinal lymphangiectasia, hypoplastic leg lymphatics, anomalous lymphatic vessels in the thoracic cage and aplasia or absence of the thoracic duct, hypoplastic inguinal and iliac lymphatic vessels, and testicular lymphangiectasis. Management of these conditions can be difficult.[131,132]

A discussion of malignant hyperthermia in patients with NS is provided in Supplemental Information.[133–137]

Table 7 lists support organizations that may serve as additional resources regarding NS.

CONCLUSIONS

These guidelines were developed from an interdisciplinary meeting of experts involved in the care of and research on individuals with NS. Our goal was to provide the pediatrician with new information and accrued experience to promote the correct diagnosis and best care of those with NS. Recognizing that NS is a clinically and genetically heterogeneous condition characterized by congenital heart disease, distinct facial features, short stature, and many other potential comorbidities, patients do require multidisciplinary evaluations and regular follow-up care for their identified issues. Certainly, many questions remain unanswered regarding the optimal care of these individuals not only in childhood but throughout adulthood. Therefore, it is important to recognize that the recommendations in this report are based on the authors' best judgments and the current available medical knowledge.

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