"Clinical features, diagnosis and management guidelines for those affected by Noonan syndrome"

A Parent's Guide to Noonan syndrome

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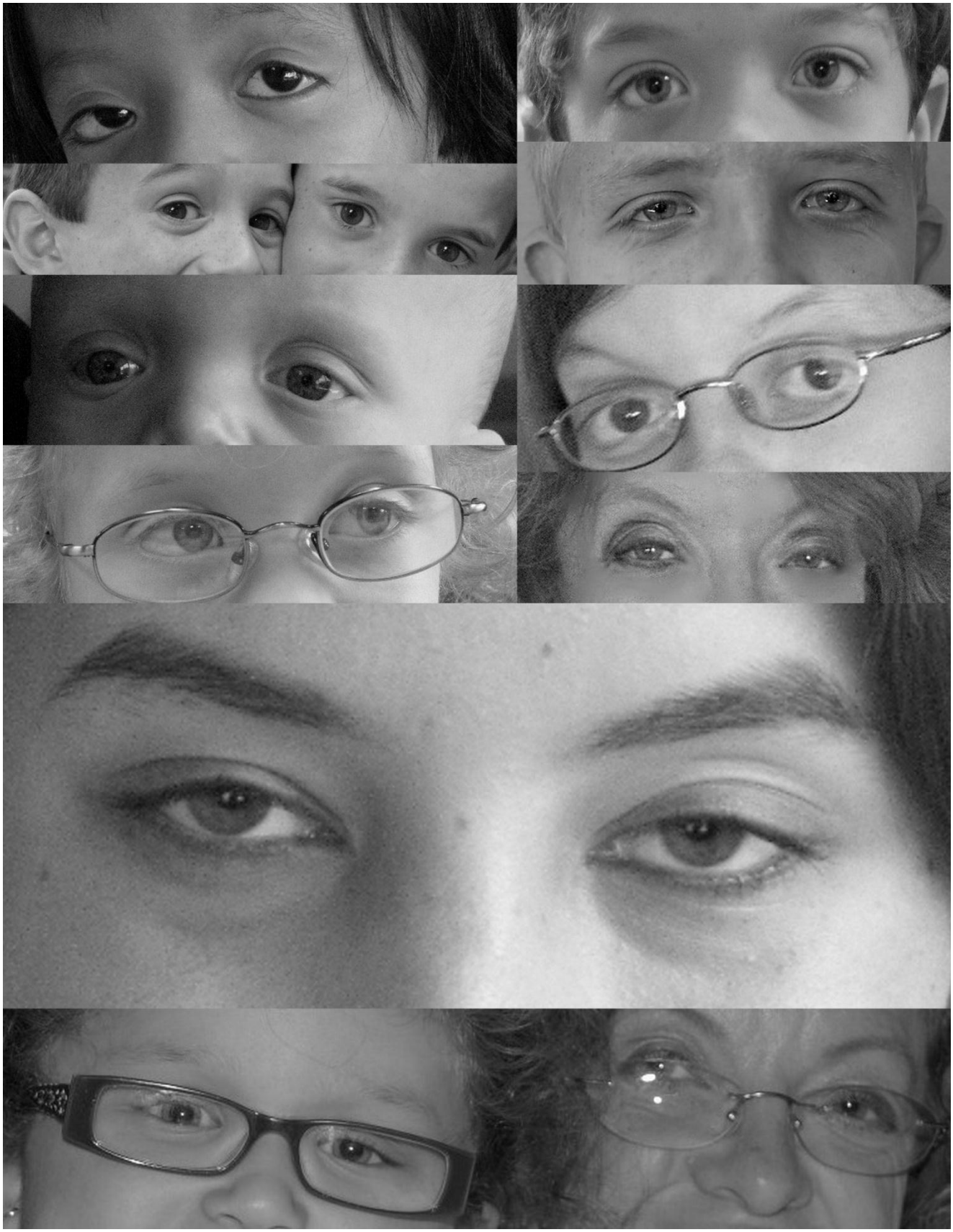
THE NOONAN SYNDROME SUPPORT GROUP, Inc.



A Parent's Guide to Noonan Syndrome

"Clinical features, diagnosis and management guidelines for those affected by Noonan syndrome"

Noonan syndrome – information for patients, relatives and others with interest in Noonan syndrome

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Abbreviations: Noonan syndrome (NS), The Noonan Syndrome Support Group (TNSSG), Ras/MAPK (mitogen activated protein kinase), Turner syndrome (TS), cardiofaciocutaneous syndrome (CFC), neurofibromatosis Type 1 (NF-1), LEOPARD syndrome (LS), fetal alcohol syndrome (FAS), protein tyrosine phosphatase, nonreceptor-type 11 gene (*PTPN11*), pulmonary valve stenosis (PVS), atrial septal defects (ASD), hypertrophic cardiomyopathy (HCM), juvenile myelomonocytic leukemia (JMML), growth hormone (GH), von Willebrand disease (vWD), von Willebrand factor (vWF), myeloproliferative disorder (MPD), Arnold-Chiari malformation, type I (ACMI), malignant hyperthermia (MH), King-Denborough syndrome (KDS), congenital myopathy
with excess of muscle spindles (CMEMS)

Abstract: Noonan syndrome (NS) is a common, predominantly inherited condition characterized by distinctive facial features, short stature, chest deformity, heart disease, and often other disease manifestations. Approximately 61% of NS cases can be explained by changes in the genetic make-up, the reason behind the remaining 39% is mostly unknown. Thus, NS frequently remains a clinical diagnosis. Because of the many different ways the condition can manifest itself and the need for multidisciplinary care, it is important that the condition be identified and managed properly and comprehensively.

The Noonan Syndrome Support Group (TNSSG) is a non-profit organization committed to providing support, current information and understanding to those affected by NS. TNSSG convened a conference of health care providers, all involved in various aspects of NS; this documents summarizes the most updated information about the condition, written in laymen terms for patients, relatives and other interested parties.

Introduction

Noonan syndrome (NS) is a relatively common inborn disorder that affects 1 in 1,000 to 1 in 2,500 live births (0.1 to 0.025% of the population). Typical findings include distinctive facial features, short stature, chest deformity, and heart disease. The disorder can be inherited and can come from either parent. Until recently, diagnosis was based solely on clinical findings but genetic testing is now used to confirm the diagnosis of

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approximately 61% of patients. Because of the difficulty in establishing a diagnosis of NS, The Noonan Syndrome Support Group (TNSSG) 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 recent information about the disease to patients with NS, relatives to patients as well as other parties interested in, or involved with, the condition.

History of Noonan Syndrome

In 1962, Jacqueline Noonan, a cardiologist specializing in heart disease in children, identified nine patients whose faces were remarkably similar and, in addition, had short stature, chest deformities and narrowing in the large pulmonary artery between the heart and the lungs. Six years later, she published a paper with these nine plus an additional ten patients. The condition was named NS in recognition of Dr. Noonan.

Dr. Kobylinski reported the first case in 1883 in a 20-year-old male with webbing of the neck. It was the webbing of the neck that attracted most early reports. In 1938, Turner reported older patients with webbing and short stature who also had sexual infantilism. Before Turner syndrome (TS) was recognized to be linked to the sex chromosome (in 1959), many cases which subsequently turned out to be NS, was classified as "male TS." This led to considerable confusion until chromosomal studies became available; then, it became apparent that a substantial proportion of girls diagnosed with TS had, in fact, NS. Some, but not all of the males, previously diagnosed as "male TS," had NS.

Clinical Description and Differential Diagnosis

It is specific features in the face and the muscular and skeletal systems that most often lead to the diagnosis of NS. The facial appearance is most characteristic in the very young child and early-to-middle childhood and becomes more subtle in adulthood. In the newborn baby, the head is large with a small face tucked beneath a large skull, a tall forehead and narrowing at the temples. The eyes are often wide-spaced and prominent with a skin fold of the upper eyelid that covers the inner corner of the eye, dropping eyelids, and horizontal or down-slanting opening between the upper and lower eyelids (95%). There is often increased distance between the eyes. The nose is short and broad with a depressed root and full tip. The ears are low-set, rotated backwards with an oval shape and thickening of the ear lobe (90%). The upper lip tends to be pretty distinctive with a deeply grooved line that runs between the middle of the upper lip to the nose and full lips (95%). Generally, the neck is short with excess skin and a low hairline (55%). In middle-to-late childhood, the facial appearance often lacks expression, resembling the face seen in individuals with muscle disorders. By adolescence, face shape is an inverted triangle, wide at the forehead and tapering to a pointed chin. Eyes are less prominent and features are sharper. There is a pinched nasal root with a thin bridge. The neck is longer, accentuating skin webbing or prominence of the big neck muscle. The adult face is often as unremarkable as the young child's face is characteristic. Some adults, however, do retain typical features including the dropping eyelids, wide-spaced eyes and low-set ears and a thickened ear lope. In the older adult, the folds between the nose and the lips are more prominent than one would expect for that person's age, and the skin often appears transparent and wrinkled.

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 and pigmentation than expected for family background.

A characteristic chest deformity with pigeon chest at the top of the chest and sunken chest at the lower part of

the chest is seen in most individuals. Also, nipples are wide-spaced and low-set and rounded shoulders are very common. A curved spine (scoliosis) is reported in 10-15%. Other less common spinal abnormalities include hunchback (kyphosis), split spine (spina bifida) and vertebral and rib abnormalities. Clubfoot is described in 10-15%. Abnormal forearm carrying angles are found in more than half the males (10-11 degrees) and females (14-15 degrees). Ability to hyperextend the forearm is also common.

Due to differences in prognosis and treatment, establishment of an accurate diagnosis is essential. There are several disorders with manifestations similar to NS, such as TS and more rare syndromes such as cardiofaciocutaneous syndrome (CFC) and Costello syndrome (Table 2). These syndromes are often confused for NS, particularly in the newborn period. There are other more rare disorders with substantial overlap with NS; however, in most cases the physician will be able to establish the correct diagnosis by a combination of clinical findings and genetic tests.

History of Molecular Genetic Testing and Genetic Research

In 1994, a large family study for the first time documented a definitive link between abnormalities on the chromosome and NS. Subsequently, it was established that the genetic manifestations were variable so that people with the same genetic abnormalities could have different clinical manifestations, and that patients with similar clinical manifestations could have different genetic abnormalities. This is called genetic variation or heterogenicity. A number of specific abnormalities in the chromosome, resulting in various defects in an enzyme named protein tyrosine phosphatase were subsequently identified.

As of this writing, six different gene errors have been identified in NS (*PTPN11*, *SOS1*, *RAF1*, *KRAS*, *NRAS* and *BRAF*), accounting for the majority of cases but there is probably one or more additional unidentified genes involved; however, rapid improvements in gene technologies should accelerate the effort in the coming years and hopefully allow identification of any remaining genes involved.

Genetic Testing for Noonan Syndrome

Commercial tests for the chromosomal abnormalities are available, there are other more rare disorders with substantial overlap with NS; however, in most cases the physician will be able to establish the correct diagnosis by a combination of clinical findings and genetic tests.

Correlations between genetic abnormality and clinical manifestations

Among the gene changes (mutations) that account for NS, there have been many different correlations made between gene abnormality and clinical manifestations. However, there have been no clear clinical characteristics found exclusively among one gene abnormality, probably due to inherited and environmental factors influencing the degree to which the gene abnormality manifest itself. There are, however, significant differences in the risk of various NS manifestations based upon the affected gene.

Certain mutations (more precisely mutations in the *PTPN11* gene) have been consistently associated with the presence of a chest deformity, easy bruising, the characteristic facial appearance, and short stature. Children with other mutations (such as *SOS1)* are more likely to have CFC syndrome-like skin findings (bumps in the skin, sparse hair, curly hair, sparse eyebrows) and less likely to have short stature or impaired memory. Patients with NS caused by changes in the *PTPN11* gene are more likely to have defects in the vascular system in the heart and less likely to have abnormal enlargement of the heart than people with NS without a *PTPN11* mutation. Remarkably, 80-95% of children with *RAF1* mutations have heart enlargement.

In a study of 45 patients with NS, bleeding disturbances as well as leukemia were found exclusively in patients with specific *PTPN11* mutations. Familial cases of NS are more likely than sporadic cases to be due to a *PTPN11* mutation. NS due to *KRAS* mutations appears to be associated with more severe disease with more significant learning issues and delays in normal development.

Cardiovascular Issues

Over 80% of patients with NS have an abnormality of the cardiovascular system. Pulmonary valve stenosis (PVS), a narrowing of the large artery pumping blood into the lungs, is the most common. PVS in these cases are often associated with an opening in the wall between the two small heart chambers (called atrial septum defect or ASD). Isolated ASD is also relatively common. A broad spectrum of cardiac abnormalities has been reported as noted in Table 3. About 50% of NS patients have an unusual ECG pattern that is not diagnostic in itself but certainly points the diagnosis towards NS. Many patients have mild PVS that requires only periodic re-evaluation. If the PVS is or becomes clinically significant, initial treatment is usually a so-called pulmonary balloon valvuloplasty, in which a catheter is introduced into the vessel and carefully navigated past the narrow spot; thereafter a balloon is inflated and used to dilate the narrow area. With severe cases, open heart surgery may be required. Most other cardiac defects can be treated with drugs or surgery.

An abnormally large heart (hypertrophic cardiomyopathy or HCM) is present in about 20% of all individuals with NS, but is particularly frequent in patients with *RAF1* mutations, and is variable in severity and natural history. In some infants with HCM the condition resolves, while in others it becomes rapidly progressive and, if left untreated, may have a fatal outcome. Others develop HCM after infancy. The course may be stable, progressive or may improve spontaneously. Management is similar to any patient with HCM and typically involves treatment with various drugs.

It is important for adults with NS to have lifetime cardiac follow-up. Lesions in the left side of the heart may develop in adulthood. Incomplete closing of the lung valve and inadequate function of the right side of the heart are potential problems following earlier lung valve surgery. Disturbances in the heart rhythm have been

noted in long-term follow-up studies of adults.

Growth and Endocrine Issues

Growth

Approximately 50 – 70 % of individuals with NS have short stature. Although short stature is a main characteristic of this condition, some individuals will have normal growth and stature. The birth weight and length are typically normal but there is a subsequent lack of normal growth so that the height and weight typically is less than the average. The mean delay of bone age is about 2 years.

Mean adult heights of European female individuals with NS is approximately 153.0 cm and for males as 162.5 cm. The mean adult height of North American individuals is 151 cm for females and 163.2 cm for males. These figures would put the average patient with NS in the lower 10% percentile of the population.

Until recently, most experience with recombinant growth hormone (rGH) in NS has been reported in studies involving small numbers of patients with varied enrollment ages, treatment duration, doses, and response. These studies have shown improved growth, without significant adverse effects.

The efficacy of rGH in NS have been evaluated in several different studies. Consistently, these studies have shown that treatment with rGH result in a mean height gain of 9.5 - 13 cm for boys and 9.0 - 9.8 cm for girls and occur with earlier initiation and longer duration of GH therapy as have been demonstrated in other conditions, such as Turners Syndrome.

Initial short-term data suggested that *PTPN11*-positive patients responded “less efficiently” to GH than the *PTPN11*-negative patients. In contrast, longer-term data comparing adult heights for those treated with GH among those who are *PTPN11* mutation-positive with those who are mutation-negative demonstrate that there is no difference in outcome.

Other Endocrine and Autoimmune Issues

Puberty is typically, although not always, delayed in both males and females with NS and is characterized by a diminished pubertal growth spurt. The mean age of pubertal onset is 13.5 -14.5 years in males and 13 -14 years in females. Puberty often progresses rapidly once it starts (< 2 years). Pubertal induction may be instituted (with careful consideration of timing for optimal height potential) for no secondary sexual characteristics in males at 14 years (testosterone induction) and females at 13 years (estrogen induction).

Renal and Genitourinary system

Renal anomalies in NS are less common (10 - 11%) and are usually of little significance. A single kidney, renal pelvis dilation, and duplicated collecting system have been reported. In up to 80% of boys, the testes do not descend normally into the scrotum and early surgery is often needed to prevent infertility. The deficient spermatogenesis that may be seen in NS is likely due to this. Fertility is not affected in females.

Hematology and Oncology Issues

Individuals with NS commonly report disordered bleeding. Although the symptoms are often mild, such as excessive bruising, nose bleed or excessive menstrual bleed, bleeding with surgical procedures can be significant. A number of coagulation factor deficiencies (isolated as well as combined), thrombocytopenia and platelet dysfunction have been described. Elevation of the APTT is frequent. Approximately 25% of individuals

with NS have partial factor XI deficiency. The bleeding symptoms do not correlate well with the degree of deficiency. A number of other coagulation factors can be depressed, with low factor XII and factor VIII activity being the next most frequent. Less commonly, factor IX and factor II have also been reported to be deficient in patients with NS, and can contribute to bleeding risk.

Both too low platelet count (thrombocytopenia), as well as platelet dysfunction has been described in NS. The etiology of the thrombocytopenia is probably multifactorial and can be associated with a defect in platelet production. An enlarged spleen (splenomegaly) may also cause mild-to-moderate thrombocytopenia and is found in up to 52% of NS patients by ultrasound. Splenomegaly may be isolated, or in association with an enlarged liver (hepatomegaly). In some patients, an enlarged liver or spleen may be due to NS/myeloproliferative disorder (NS/MPD), a syndrome often seen in infants with NS and characterized by increased number of white blood cells, thrombocytopenia and enlarged liver and spleen. Although the clinical picture of NS/MPD resembles that of certain leukemia's, infants with NS/MPD appear to have a favorable prognosis. The majority of children with this condition present in the first few months of life and will remain stable or improve by a year of age without specific therapy.
The incidence of cancer in patients with NS does not appear to be increased over the general population.

Neurological, Learning, and Behavioral Issues

The neurological, learning, and behavioral aspects of NS individuals are poorly understood and extremely variable. There is an increased incidence of learning disabilities, an increased incidence of brain abnormalities and a wide array of other neurological problems. In a study of 151 cases, 76% had feeding difficulties, 94% problems with their eyes, 50% increased mobility of joints or reduced muscle tone, 13% recurrent seizures, 3% hearing loss and 3% peripheral neuropathy. There was also a general delay in normal developmental milestones with sitting alone occurring at 10 months, walking at 21 months and two word sentences at 31 months. Other studies have found that up to 84% had some type of neurological problem.

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 (ACMI) and hydrocephalus. The mean head circumference is 50th percentile; however, some NS individuals can have abnormal small or abnormal big head circumference.

Most have normal intelligence, but 10-40% requires special education. Even among those of normal intelligence, their IQ was 10 points less than unaffected family members. NS children have a higher rate of clumsiness, coordination, stubbornness, and irritability. Body image problems with poor self-esteem, depression, and social inadequacy have been noted in adult NS individuals. Despite these problems, the majority of adult NS individuals finished high school and had paying jobs.

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 requiring tube feeding for 2 weeks or more are common (24%). Investigation of some children with poor feeding has documented immaturity of gut motility and delayed gastrointestinal development. Gastroesophageal reflux is common, and there are a few reports of malrotation. Typically, the period of failure to thrive is self-limiting, although poor weight gain may persist for up to 18 months.

Oral and Dental Issues

Oral findings in NS include a high arched palate (55-100%), dental malocclusion in half to two-thirds of the patients and articulation difficulties (72%). Some NS individuals develop cysts in the lower jaw, which can mimic cherubism, a syndrome with very square features in the lower half of the face.

Lymphatic Issues

NS is associated with a generalized disorder of the lymph system, which has manifestations in fetal life through adulthood. The overall incidence of lymphatic manifestations in all age groups of NS is approximately 20%. Accumulation of lymph in arms and legs (peripheral lymphedema) are the most common lymphatic manifestations, and most frequently seen in young infants. Typically it resolves in the first few years of life. Adolescents and adults can also develop peripheral lymphedema.

Malignant Hyperthermia

The risk of malignant hyperthermia (MH) is near or at the population rate among patients with NS. This conclusion was derived from a thorough literature review, CPK levels in NS, congenital myopathy with excess of muscle spindles (CMEMS) and the lack of reported cases of MH in NS considering the vast number of patients with NS that have undergone procedures with general anesthesia.

Conclusion

This paper was developed from an interdisciplinary meeting of experts involved in the care of and research on individuals with NS. Their goal was to provide NS patients and their families with the most recent information and knowledge about their disease. Recognizing that NS is a clinically and genetically heterogeneous condition characterized by congenital heart disease, distinct facial features, short stature, and many other potential co-morbidities, 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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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: o Positive gene testing can confirm NS diagnosis o Negative tests cannot exclude the diagnosis o Expected frequency of mutations among patients with definite NS by sequencing the six genes known to date is approximately 61% ▪ If sequential molecular testing is determined to be indicated (rather than simultaneous chip based analysis): o *PTPN11* sequencing should be done first as this gene explain the highest number of cases o If normal, phenotype should be used to guide the choice of the next gene to sequence o If developmental delays absent or mild, CFC-like skin and hair findings present and/or normal stature, consider *SOS1* sequencing o If HCM is present, consider *RAF1* sequencing o For significant developmental delays or cognitive issues, consider *KRAS* sequencing. o 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. This includes a chest x-ray, ECG 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 <u>should not be</u> discontinued. ▪ Individuals without heart disease on their initial evaluation should have cardiac re-evaluation every 5 years. ▪ 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 & Endocrine Issues	▪ Children should be weighed and measured regularly by the primary care provider and plotted on appropriate growth charts (Thrice yearly for the first 3 years of life, and yearly thereafter). ▪ Children with evidence of growth failure (growth deceleration, height < -2 SD, or height inappropriate for genetic background) that cannot be explained by a comorbidity should be monitored more often, have nutrition optimized, have baseline labs obtained and/or referred to a Pediatric Endocrinologist. ▪ Thyroid function tests and antibodies should be obtained in 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 age 13 years, no testicular enlargement in boys by age 14 years) should be referred to a Pediatric Endocrinologist ▪ Therapeutic interventions as indicated (growth hormone for growth failure, thyroid hormone replacement for hypothyroidism, estrogen or testosterone for pubertal delay)

Renal & Genitourinary Issues	▪ All individuals should have a kidney ultrasound at the time of diagnosis, with possible need to repeat depending on initial findings ▪ Individuals may be at increased risk of urinary tract infections (UTI) if a structural abnormality is present ▪ Antibiotic prophylaxis may be considered for hydronephrosis and/or recurrent UTI ▪ Orchiopexy should be performed by age one year if testicles remain undescended at that time
Gastrointestinal Issues	▪ Pediatric Gastroenterology/ Nutrition Consultation for feeding difficulties/ recurrent vomiting ▪ Further testing as indicated (upper GI series, upper endoscopy, pH studies, etc)) ▪ Therapeutic interventions as indicated (anti-reflux medications, feeding therapy, feeding tube, surgical consult if malrotation suspected, etc)
Hematology Issues	▪ Screening CBC with differential and PT/aPTT at diagnosis and after 6-12 months of age if initial screen performed in infancy ▪ Bleeding symptoms: o *First tier* - CBC with differential count and PT/aPTT o *Second tier* (in consultation with hematologist) -specific factor activity (FXI, FXII, FIX, FVIII, vWF, 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 & Behavioral Issues	▪ Developmental Screening annually ▪ Complete Neuropsychological testing if screening abnormal ▪ Evaluations for speech pathology, physical therapy (PT) and occupational therapy (OT) if delays in speech, gross motor and fine motor skills, respectively ▪ Early intervention programs beginning in infancy if delays noted ▪ Speech therapy (ST) 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 age children ▪ EEG and referral to Neurology if seizures suspected ▪ Brain and upper spine MRI with any neurological problem (headaches, weakness, numbness, poor balance, etc), cranial size aberration ▪ MRA (after MRI) if focal/sudden neurological signs
Eye & Ear Issues	▪ Detailed eye examination in infancy and/or at diagnosis ▪ Eye re-evaluations as indicated if problems found or at least every 2 years 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 & Dental Issues	▪ Annual examination of chest & back, x-rays if abnormal ▪ Careful oral exam at each visit ▪ Dental referral between age 1 and 2 years with yearly visits thereafter ▪ Dental x-rays 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 (MH) when receiving general anesthesia. ▪ Avoidance of anesthetics associated with MH in those individuals with NS-like phenotype, a skeletal myopathy and a normal to modestly elevated CPK and HCM. ▪ Skeletal muscle biopsy should be considered to look for excess muscle spindles (suspect diagnosis of CMEMS: congenital myopathy with excess muscle spindles) in those with NS-like phenotype, a skeletal myopathy and a normal to modestly elevated CPK and HCM.

Table 2: Differential Diagnosis: Similarities and differences between NS and other disorders

Syndrome	Similarities with NS	Differences with NS
Aarskog syndrome (AS) (Faciogenital dysplasia)	Similarities in NS and AS are primarily facial and skeletal (hypertelorism, down slanting palpebral fissures, and short stature).	In AS: No cardiovascular malformations but shawl scrotum present. This is an X linked recessive disorder caused by *FGD1* gene mutations.
Baraitser-Winter syndrome	Common features to both NS and Baraitser-Winter syndrome include hypertelorism, eyelid ptosis, short neck, short stature, and cognitive delays.	In Baraitser-Winter syndrome: There can be iris coloboma, pachygyria, lissencephaly, bicuspid aortic valve, and aortic stenosis.
Cardiofaciocutaneous syndrome (CFC)	Common facial, skeletal, and cardiac features in both NS and CFC include hypertelorism with down slanting palpebral fissures, epicanthal folds and eyelid ptosis, depressed nasal root, short stature, relative macrocephaly, pulmonary valve stenosis, HCM, and ASD. *KRAS* or *BRAF* mutations have been seen in both NS and CFC.	In CFC: Coarser facial features, severe feeding problems, follicular hyperkeratosis, sparse eyebrows and eyelashes, ichthyosis, ulerythema ophyrogenes. Majority have moderate retardation. May be caused by *MEK1* or *MEK2* mutations.
Costello syndrome (CS)	Many features common to both CS and NS include curly hair, wide nasal bridge, eyelid ptosis, down slanting palpebral fissures, epicanthal folds, pulmonary valve stenosis, HCM, pectus deformity, and Chiari I malformation.	In CS: 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. Caused by *HRAS* mutations.
Fetal Alcohol syndrome (FAS)	Common features to both NS and FAS include growth delay, developmental delay, hypertelorism, epicanthal folds, pulmonary valve stenosis, and atrial septal defect.	In FAS: Born small for gestational age, have 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 (LS)	Common features to LS and NS include hypertelorism, pulmonary valve stenosis, hypertrophic cardiomyopathy, short stature, caused by *PTPN11, RAF1, or BRAF* gene mutations	In LS: 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.
Neurofibromatosis Type 1 (NF-1)	Some people with NF-1 gene mutations have NS-like facial features and	In NF-1: Multiple café au lait, axillary and inguinal freckling, cutaneous

	pulmonary valve stenosis	neurofibroma, iris Lisch nodules
Turner syndrome (TS)	Girls with NS and TS can have short stature, eyelid ptosis, increased internipple distance, webbed neck, and kidney malformations.	Cardiac features typically left sided in TS, right sided in NS Coarctation of the aorta and/or bicuspid aortic valve more characteristic of TS. Girls have gonadal dysgenesis in TS; normal fertility in females with NS. TS is due to loss of one copy of the X chromosome.

Table 3: Cardiac conditions in Noonan syndrome

Frequent	Occasional	Rare
Pulmonary valvular stenosis	Aortic valvular stenosis	Pulmonary hypertension
Secundum atrial septal defect	Supravalvular pulmonary stenosis	Aortic root dilation
Hypertrophic cardiomyopathy	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	

Table 4: Baseline and treatment growth data from studies reporting adult height outcomes in individuals with NS treated with GH.

Patients, n, (sex)	Baseline Age (years)	Baseline SDS *	GH Dose	Duration therapy (years)	Delta Ht SDS	Ht Gain
4 (4 F)	13.5	(- 0.6)	0.19 mg/kg/wk x 1 yr, then 0.31 mg/kg/wk)	3.5	(0.48)	NA
10 (4 F)	12	-3.1 (-0.7)	0.30 mg/kg/wk	5.3		3.1 cm
18(11F)	8.6 (M) 7.7 (F)	-2.9 (-0.3)	0.23 mg/kg/wk (n = 10), 0.46 mg/kg/wk (n = 15) x 2 yrs then dose titration Estimated mean 0.35 mg/kg/wk	7.5	1.7	13 cm (M), 9.8 cm (F)
24 (NA)	10.2 (median)	-3.24 (median)	0.24 mg/kg/wk (median) Range: (0.17 – 0.77 mg/kg/wk)	7.59 median	0.61 (0.97)	NA
29 (8 F)	11	-2.8 (0.0)	0.35 mg/kg/wk	6.4 median	1.3 (1.3)	9.5 cm (M), 9.0 cm (F)
65 (30F)	11.6	-3.5	0.33 mg/kg/wk	5.6	1.4	10.9 cm (M) 9.2 cm (F)

*Height SDS reported according to population standards and/or (NS standards). SDS = standard deviation score; Ht = height; M = male; F = female **.** Results are mean values unless specified otherwise.

Table 5: Support Organizations for NS

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

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