

Management of Noonan Syndrome

A Clinical Guideline

Noonan Syndrome Guideline Development Group



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Introduction...

... to Noonan Syndrome (NS)

Noonan syndrome (NS) is one of the more common genetic conditions.

The incidence of NS is estimated as 1 in 1,000 to 1 in 2,500 births, so it is still a relatively rare condition.

The severity of NS is the same in males and females.

The main features are congenital heart defects, short stature and characteristic facial features.

Early motor delay associated with hypotonia is not necessarily associated with later learning difficulty, and most adults with NS are able to lead independent autonomous lives.

... to the Noonan Syndrome Guideline Development Project

The guidelines have been developed using a robust methodology based on the one utilised by the Scottish Intercollegiate Guidelines Network (SIGN). The method has been adapted to suit rare conditions where the evidence base is limited, and where expert consensus plays a greater role. The members of the guideline development group are listed on page 30.

... to the Noonan Syndrome Clinical Management Guidelines

What are the aims of the guidelines?

The guidelines aim to provide clear and wherever possible, evidence-based recommendations for the management of patients with Noonan syndrome.

Who are they aimed at?

These guidelines are provided for people with NS to use with their primary care and specialist clinicians as many healthcare professionals will not have had personal experience of managing Noonan syndrome. As it is a multisystem disorder, people with NS may require various tests, screening, assessments, referrals and multidisciplinary interventions at different stages of their lives. These guidelines lay out these requirements in a clear format that is accessible to anybody who is involved in the care of an individual with NS.

How are they organised?

The guidelines are divided into recommendations for four age groups:

- Neonatal and Infancy—0—1 years old - Childhood: 1—11 years old - Adolescence: 11—18 years old - Adulthood: 18 years old +

Page 4 contains an overview of the diagnostic criteria and clinical features of NS, and page 5 lists the suggested baseline investigations. Subsequently, the guidelines are organised into specific age groups. For each group, management issues along with any recommended tests/screenings are listed, and follow-up options depending on the outcome of the test or screening are indicated.

NB. ABNL= Abnormal

A full list of references starts on page 19, organised by body system, which can be used as a signpost to further information on specific aspects of NS for healthcare professionals.

Additionally, there is a list of useful contacts for parents and families affected by NS, on page 29.

Diagnosis and clinical features of Noonan Syndrome

Diagnostic features of NS (van der Burgt 1997)

Feature	A = Major	B = Minor
1. Facial	Typical face (Facial features of NS vary over time and may have only subtle differences. Expert assessment is therefore Required. See Allanson 1987—full reference p.19).	Suggestive face
2. Cardiac	Pulmonary valve stenosis and/or hypertrophic cardiomyopathy (HCM)	Other cardiac defect
3. Height	< 3th centile	< 10th centile
4. Chest wall	Pectus carinatum/excavatum	Broad thorax
5. Family History	First degree relative with definite NS	First degree relative suggestive of NS
6. Other	Mild developmental delay, cryptorchidism AND lymphatic dysplasia	Mild developmental delay, cryptorchidism, OR lymphatic dysplasia

Definitive NS:

Criterion 1A +		Criterion 1B +	
One of 2A—6A	Two of 2B—6B	Two of 2A—6A	Three of 2B—6B

*Currently, mutation testing will prove a diagnosis of Noonan Syndrome in 70% of cases; in 30% the responsible gene remains unknown.
 The diagnosis of NS should be considered in parents when a child is diagnosed with the syndrome.
 Given the number of different genes where mutations can cause NS, the appropriateness and sequence of gene testing should be decided by a clinical geneticist.

Differential diagnoses:

- Cardio-facio-cutaneous syndrome (CFC)
- Costello syndrome
- LEOPARD syndrome
- King-Denborough Syndrome (phenotypically distinct. Malignant hyperthermia is not described in NS)

NB—Neurofibromatosis-Noonan syndrome formed part of the differential diagnosis in the past; it is now known that some patients with either of these conditions will have overlapping clinical features, due to the causative mutations occurring in the same biological pathway.

Recommended baseline investigations in Noonan Syndrome

Clinical Features of Noonan Syndrome		Baseline investigations
(where an investigation is not indicated for a specific clinical feature, please refer to the relevant age group-specific page for management recommendations)		
• Congenital heart defects (e.g. pulmonary stenosis, hypertrophic cardiomyopathy, atrial septal defect)	→	• Full cardiac evaluation at diagnosis.
• Failure to thrive/slow growth rate/feeding problems	→	• Monitor and plot growth on appropriate NS and age-based growth chart.
• Short stature	→	
• Developmental delay and neuropsychological/behavioural issues	→	• Refer patient in second half of first year or at diagnosis for formal developmental assessment. • Baseline neuropsychological assessment at primary school entry.
• Minor renal anomalies	→	• Refer for renal ultrasound at diagnosis.
• Bleeding disorders	→	• Carry out baseline coagulation screening in patients aged 5+, or earlier if major procedure to be undertaken. (Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPPT) and FXI assay.)
• Visual problems (e.g. posterior segment ocular changes and anterior segment ocular abnormalities)	→	• Refer for specialist ophthalmology assessment at the point of diagnosis.

Recommendations for the management of Noonan Syndrome

~ in neonates & infancy (1) ~

AGE 0—1

Recommended Testing/Screening		Clinical Management Recommendations
• Feeding assessment		Refer for dietary assessment and evaluation of swallowing if needed.
		Refer to speech therapist for management if necessary.
		Frequent vomiting should prompt investigation for gastro-oesophageal reflux and malrotation.
		Treat with anti-reflux measures. Persistent vomiting or food refusal may require tube feeding (although this is rare).
• Full cardiac evaluation		At diagnosis.
		If hypertrophic cardiomyopathy (HCM) is found, follow up carefully. Management of congenital heart disease is as per the general population, however a dysplastic valve is more likely and therefore surgery may be more likely to be necessary.
• Growth monitoring		Measure height, weight and occipitofrontal circumference (OFC) at birth and 1-3 monthly. Plot on NS-specific growth charts.
		Routine paediatric investigations for failure to thrive and reduced growth velocity.
• Neuropsychological and Behavioural Issues		Refer for formal developmental assessment in 2nd half of first year.
		Developmental delay caused by hypotonia will improve with occupational and physiotherapy. Management of developmental delay will be as per the general population.
• Neurology —potential complications in NS include seizures, craniosynostosis, hydrocephalus and Arnold Chiari Malformation.		Low threshold for investigation of neurological symptoms e.g. consider Arnold-Chiari malformation and hydrocephalus if patient presents with headache or other neurological symptoms, and refer for MRI if suspected.
• Renal ultrasound		Refer to paediatric nephrologist for management if renal anomalies are identified in ultrasound at diagnosis.

Recommendations for the management of Noonan Syndrome

~ in neonates & infancy (2) ~

AGE 0—1

Recommended Testing/Screening

- **Coagulation screening**
- **Check for cryptorchidism**
- **Skin problems:**
Keratosis Pilaris/Ulerythema
- **Genetic mutation screening**
- **Vision screening:** squint, posterior segment ocular changes and anterior segment ocular abnormalities have been described in NS.
- **Hearing assessment**



ABNL



ABNL



ABNL



ABNL

Clinical Management Recommendations

- To be carried out before any major surgery in neonates/infants, and at least once during childhood.
- Manage in the standard way at the appropriate time.
- Avoid skin dryness, which can be worsened by long hot baths, perfumed soaps and dry atmospheres.
- Manage using emollients, keratolytic agents e.g. salicylic acid in urea cream, if tolerated, or short courses of topical steroids if necessary (especially if erythematous).
Within a specialist dermatology setting, it should be noted that retinoids may not be a first choice treatment as they have been shown not to work in some NS patients.
- Should be considered in the context of genetic management—which genes are tested for should be decided by a clinical geneticist.
- Refer for baseline evaluation at point of diagnosis.
- Ophthalmic follow up/management as deemed appropriate by the ophthalmologist.
- Refer for baseline evaluation in 2nd half of first year.
- Management in standard way.

! Anaesthesia

NS can cause coagulation difficulties that should be evaluated prior to surgical procedures so that care, including anaesthesia, can be planned accordingly.

Patients with NS and haemodynamically significant cardiac involvement such as severe hypertrophic cardiomyopathy need to be treated according to the usual principles for patients with such cardiovascular risk factors.

Patients with NS may have craniofacial and/or vertebral anomalies that could affect intubation or the administration of spinal anaesthesia.

Recommendations for the management of Noonan Syndrome ~ in childhood (1) ~

AGE **1—11**

Recommended Testing/Screening

• Echocardiogram (ECHO)



ABNL



• Growth assessment



Growth hormone (GH) axis evaluation



GH & hypertrophic cardiomyopathy (HCM)



• Coagulation screening



Clinical Management Recommendations

Annually until the age of 3 and then at 5 and 10 years old, to assess for onset of HCM.

If results indicate HCM, follow-up regularly.

Management of congenital heart disease is as per the general population, however a dysplastic valve is more likely and surgery may be more likely to be necessary.

If ECHO results are normal at the age of 10 years old and older, cardiac follow up remains necessary due to the ongoing increased risk of cardiomyopathy.

Nearly half of children with NS will reach a height within the normal range without growth hormone (GH) intervention.

Modest response to growth hormone therapy (GHT) has been documented but some NS patients will continue to grow into their late teens/early twenties (because of late puberty) and thereby reach normal range.

Final height may also be influenced by parental height.

Plot growth on NS growth charts.

All children with a height below the mean for NS should be referred to a paediatric endocrinologist for assessment.

If height is below 2.5 standard deviations (SD) from the mean on standard childhood charts, GHT may be considered without evaluation of the GH axis.

If IGF-1 levels are low, testing of the GH axis should be considered to show growth hormone deficiency (GHD).

NB. While many consider existing HCM or malignancy as relative contraindications to GHT, there are no data to support this claim.

Additionally, there is no evidence of an increased risk of HCM or malignancy developing in people with NS undertaking GHT.

Should be carried out at least once during mid/late childhood (5—11 years old), and before major surgery.

Aspirin should be withheld before any surgical interventions, as per standard practice.

Recommendations for the management of Noonan Syndrome ~ in childhood (2) ~

AGE **1—11**

Recommended Testing/Screening

- **Neuropsychological and Behavioural Issues:** hypotonia and motor delay are common in NS and can cause developmental delay.
- **Neurology**—potential complications in NS include seizures, craniosynostosis, hydrocephalus and Arnold Chiari Malformation.
- **Musculoskeletal**
- **Feeding assessment:** if necessary—most feeding issues will have resolved by 18 months.
- **Check for cryptorchidism**
- **Lymphoedema:** There is an increased risk of developing lymphoedema in NS, throughout childhood and later life.

Clinical Management Recommendations

Screening for developmental delay and full neuropsychological assessment at primary (to include speech acquisition) and secondary school entry, and if/when symptomatic.
Assess intellectual/cognitive abilities with special attention for learning difficulties as a result of motor delay, executive dysfunctions and inattention.

ABNL Developmental delay caused by hypotonia will improve with occupational and physiotherapy.
Referral for speech therapy if acquisition is delayed.
Management of developmental delay will be as per the general population.
Ongoing review and support of learning and development with further assessment of special educational needs as required.

Low threshold for investigation of neurological symptoms e.g. consider Arnold-Chiari malformation and hydrocephalus if patient presents with headache or other neurological symptoms, and refer for MRI if suspected.

Monitor for scoliosis. Be aware that it can worsen with GHT.

ABNL Talipes occurs in 5 % of NS patients and should be managed as per the general population.

ABNL Refer for occupational therapy for management of hypermobility.

ABNL Refer for dietary assessment and evaluation of swallowing if needed.

ABNL Refer to speech therapist for management if necessary.

ABNL Frequent vomiting should prompt investigation for gastro-oesophageal reflux and malrotation.

ABNL Treat with anti-reflux measures. Persistent vomiting or food refusal may require tube feeding (although this is rare).

ABNL Manage in the standard way at the appropriate time.

ABNL Management should be the same as for general population.

Recommendations for the management of Noonan Syndrome ~ in childhood (3) ~

AGE **1—11**

Recommended Testing/Screening

- **Skin problems:**
Keratosis Pilaris/Ulerythema
- **Vision screening:** squint, posterior segment ocular changes and anterior segment ocular abnormalities are frequent in NS.
- **Hearing assessments:** NS patients have an increased risk of conductive hearing loss. Sensorineural hearing loss is rare but has been described.
- **Dental screening**

Giant cell lesions of the jaw

Clinical Management Recommendations

Avoid skin dryness, which can be worsened by long hot baths, perfumed soaps and dry atmospheres.

Manage using emollients, keratolytic agents e.g. salicylic acid in urea cream, if tolerated, or short courses of topical steroids if necessary (especially if erythematous).
Within a specialist dermatology setting, it should be noted that retinoids may not be a first choice treatment as they have been shown not to work in some NS patients.

Unless already under ophthalmic management, NS patients should be referred to an ophthalmologist for assessment if/as appropriate.

Monitor hearing annually from 1—11 years old to prevent speech development problems.

Published evidence on the management of routine dental problems in NS is limited. Enrol patient in an individualised preventative oral healthcare programme from an early age.
Routine follow up and regular dental examinations by a family dentist or local community dental services are essential.

Missing teeth/malocclusion/other dental anomalies: refer to a consultant in paediatric dentistry for multidisciplinary management.

Refer to Oral/Maxillofacial/Head & Neck Surgeon or expert dental care centre.

! Anaesthesia

NS can cause coagulation difficulties that should be evaluated prior to surgical procedures so that care, including anaesthesia, can be planned accordingly.

Patients with NS and haemodynamically significant cardiac involvement such as severe hypertrophic cardiomyopathy need to be treated according to the usual principles for patients with such cardiovascular risk factors.

Patients with NS may have craniofacial and/or vertebral anomalies that could affect intubation or the administration of spinal anaesthesia.

Recommendations for the management of Noonan Syndrome ~ in adolescence (1) ~

AGE **11—18**

Recommended Testing/Screening		Clinical Management Recommendations
• Echocardiogram (ECHO)	→	An ECHO in adolescence is recommended as this is when familial HCM may first be identified.
	→	Continued cardiac follow up throughout adolescence is important.
• Puberty	→	The likelihood of delayed puberty should be anticipated, and appropriate education and counselling provided around this issue.
• Neuropsychological and Behavioural Issues	→	Access to social skills training, and programmes to teach basic self help and daily living skills, if required.
	→	Screen for mood and anxiety disorders if suspected.
	ABNL →	If necessary, consider pharmacological management.
• Neurology —potential complications in NS include seizures, craniosynostosis, hydrocephalus and Arnold Chiari malformation)	→	No routine screening is recommended, however there should be a low threshold for investigation of neurological symptoms e.g. consider Arnold-Chiari malformation and hydrocephalus if patient presents with headache or other neurological symptoms, and refer for MRI if suspected.
	ABNL →	Management of specific complications, including epilepsy, will be as per the general population.
• Coagulation screening	→	Screen before any surgical intervention, and withhold aspirin prior to surgery, as per standard practice.
• Musculoskeletal	→	Monitor for scoliosis.
	→	Be aware that scoliosis can worsen with GHT and in adolescence.
• Thyroid screening	→	Screen blood for thyroid abnormalities every 3—5 years in older children and adults.
	ABNL →	Manage anomalies as in general population.
• Lymphoedema	→	There is an increased risk of developing lymphoedema in NS, throughout childhood and later life.
	ABNL →	Management should be the same as for general population.

Recommendations for the management of Noonan Syndrome ~ in adolescence (2) ~

AGE **11–18**

Recommended Testing/Screening

- **Skin problems:**
Keratosis Pilaris/Ulerythema



Clinical Management Recommendations

Avoid skin dryness, which can be worsened by long hot baths, perfumed soaps and dry atmospheres.

Manage using emollients, keratolytic agents e.g. salicylic acid in urea cream, if tolerated, or short courses of topical steroids if necessary (especially if erythematous).

Within a specialist dermatology setting, it should be noted that retinoids may not be a first choice treatment as they have been shown not to work in some NS patients.

- **Vision screening:** squint, posterior segment ocular changes and anterior segment ocular abnormalities have been described in NS.



Unless already under ophthalmic management, NS patients should be referred to an ophthalmologist for assessment if/as appropriate.

- **Dental screening**



Published evidence on the management of routine dental problems in NS is limited. Routine follow up and regular dental examinations by a family dentist or local community dental services are essential.



Missing teeth/malocclusion/other dental anomalies: refer to a consultant in paediatric dentistry for multidisciplinary management.

Giant cell lesions of the jaw



Refer to Oral/Maxillofacial/Head & Neck Surgeon or expert dental care centre.

- **Genetic counselling**



Refer for genetic counselling, mutation testing and discussion of risks to children and options in pregnancy, at an appropriate time.

! Anaesthesia

NS can cause coagulation difficulties that should be evaluated prior to surgical procedures so that care, including anaesthesia, can be planned accordingly.

Patients with NS and haemodynamically significant cardiac involvement such as severe hypertrophic cardiomyopathy need to be treated according to the usual principles for patients with such cardiovascular risk factors.

Patients with NS may have craniofacial and/or vertebral anomalies that could affect intubation or the administration of spinal anaesthesia.

Recommendations for the management of Noonan Syndrome ~ in adulthood (1) ~

AGE **18+**

Recommended Testing/Screening	Clinical Management Recommendations
• Genetic counselling	Refer for genetic counselling, mutation testing and discussion of risks to children and options in pregnancy.
• Fertility issues	Care providers should be made aware of the increased risk of infertility in males with NS, and not just in those with cryptorchidism. Refer to a fertility clinic or endocrinologist if necessary.
• In pregnancy	Prenatal features include; polyhydramnios, increased nuchal translucency, hydrops fetalis and cystic hygroma, with or without associated ascites, pleural effusion, renal abnormalities and congenital heart defects.
Fetal considerations	Chorionic villus sampling (CVS) or amniocentesis is possible—referral to a clinical genetics service preconceptually is ideal— if parental mutation is known and couple wish for a prenatal diagnosis.
Maternal considerations	Ultrasounds at 12—14 and 20 weeks and undertake mutation analysis if parental mutation known and clinical features are suggestive, if required. Potential difficulties, for example those arising from coagulation defects during childbirth, should be considered and planned for as appropriate.
• Neuropsychological and Behavioural Issues	Repeat neuropsychological assessment if patient is symptomatic of mood/anxiety disorder(s), or if cognitive impairments are suspected. Pay extra attention to the evaluation of social cognition and social embedding. Consider the risk of under-diagnosing because of problems in expressing emotions. If necessary, consider pharmacological management. Facilitate access to support for employment, self help and independent living. Social skills intervention as needed.
• Neurology —potential complications in NS include seizures, craniosynostosis, hydrocephalus and Arnold Chiari malformation)	Low threshold for investigation of neurological symptoms e.g. consider Arnold-Chiari malformation and hydrocephalus if patient presents with headache or other neurological symptoms, and refer for MRI if suspected.
• Coagulation screening	Management of specific complications, including epilepsy, will be as per the general population.
• Cardiac screening	Screen before any surgical intervention, and withhold aspirin prior to surgery, as per standard practice.
Pulmonary artery intervention	Newly diagnosed adults: full cardiac evaluation including ECHO. Previously diagnosed adults: regular cardiac assessment of existing heart disease, or cardiac evaluation incase aortic disease missed previously. Follow up for pulmonary valve insufficiency.

Recommendations for the management of Noonan Syndrome ~ in adulthood (2) ~

AGE **18+**

Recommended Testing/Screening

• Thyroid screening



Screen blood for thyroid abnormalities every 3—5 years.

ABNL

Manage anomalies as in general population.

• Lymphoedema



There is an increased risk of developing lymphoedema in NS, throughout adulthood.

ABNL

Management should be the same as for general population.

• Skin problems: Keratosis Pilaris/Ulerythema



Avoid skin dryness, which can be worsened by long hot baths, perfumed soaps and dry atmospheres.

ABNL

Manage using emollients, keratolytic agents e.g. salicylic acid in urea cream, if tolerated, or short courses of topical steroids if necessary (especially if erythematous).



Within a specialist dermatology setting, it should be noted that retinoids may not be a first choice treatment as they have been shown not to work in some NS patients.

• Vision screening: squint, posterior segment ocular changes and anterior segment ocular abnormalities have been described in NS.



Unless already under ophthalmic management, NS patients should be referred to an ophthalmologist for assessment if/as appropriate.

• Dental screening



Published evidence on the management of routine dental problems in NS is limited.

ABNL

Routine follow up and regular dental examinations by a family dentist or local community dental services are essential.

ABNL

Missing teeth/malocclusion/other dental anomalies: refer to a consultant in dentistry for multidisciplinary management.

Giant cell lesions of the jaw



Refer to Oral/Maxillofacial/Head & Neck Surgeon or expert dental care centre.

! Anaesthesia

NS can cause coagulation difficulties that should be evaluated prior to surgical procedures so that care, including anaesthesia, can be planned accordingly.

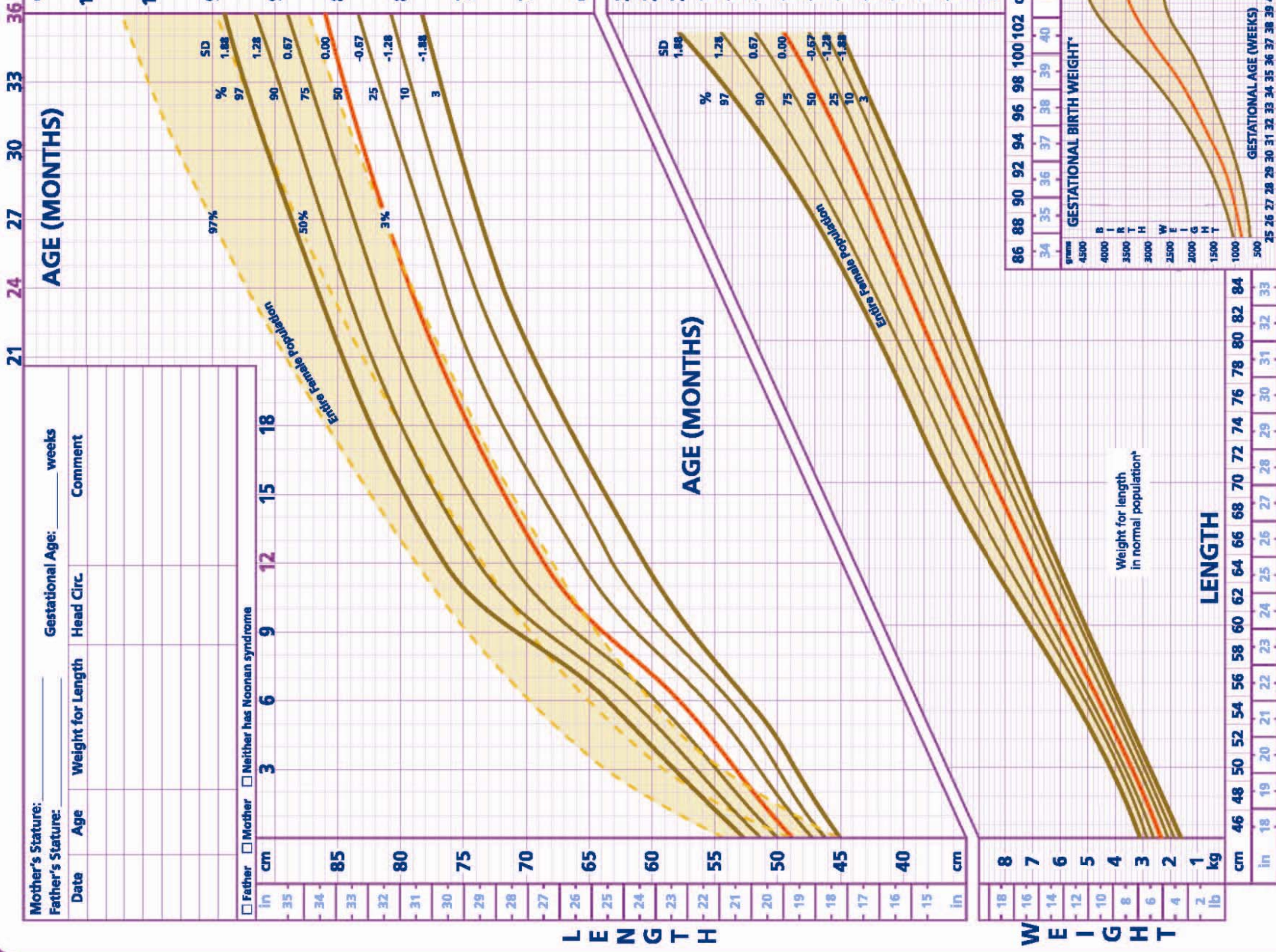
Patients with NS and haemodynamically significant cardiac involvement such as severe hypertrophic cardiomyopathy need to be treated according to the usual principles for patients with such cardiovascular risk factors.

Patients with NS may have craniofacial and/or vertebral anomalies that could affect intubation or the administration of spinal anaesthesia.

NOONAN SYNDROME GIRLS

Length for Age and Weight for Length^{a,b}

DOB: _____ ID: _____



Charts created with data from: Ranke, et al. *Eur J Pediatr*; 1988;148(3):220-227. Usher, et al. *J Pediatr*; 1969;74(6):901-910. Witt, et al. *Clin Genet*; 1986;30:150-153.

Plot points taken from data available at <http://www.cdc.gov/nchs/data/naehs/growthcharts/zscore/lenagelnt.xls> and <http://www.cdc.gov/nchs/data/naehs/growthcharts/zscore/wlenint.xls>.

% = population percentile
SD = standard deviation



Stature and Growth Velocity for Age^a

DOB: _____ ID: _____



cm	3	4	5	6	7	8	9
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Charts created with data from: Ranke, et al. *Eur J Pediatr* 1988;148(3):220-227. Tanner, et al. *J Pediatr* 1985;107(3):317-329. Usher, et al.

Plot points taken from data available at:
<http://www.cdc.gov/nchs/data/haanes/growthcharts/stage.txt>.

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Information for Parents

Sources of Information and Support

Support for parents and other family members is cited in the literature as being an important provision for families affected by NS. The groups listed below are useful sources of support and information.

- **The Noonan Syndrome Support Group, Inc. (www.noonansyndrome.org)**

The Noonan Syndrome Support Group is an international organisation, based in the US, that aims to support families affected by NS all over the world.

They offer information, support, and networking opportunities, and aim to improve awareness of NS and fund research into various aspects of the condition.

They regularly broadcast webchats with medical experts in NS, and run a well-used discussion forum.

For more information, or to join the Support Group, visit their website.

- **Contact a Family (www.cafamily.org.uk)**

The Contact a Family website is for families who have a disabled child and whose who work with then or are interested to find out more about their needs. Contact A Family is the only UK charity providing support and advice to parents whatever the medical condition of their child, they have information on over 1,000 rare syndromes and can often put families in touch with each other.

- **Orphanet (www.orpha.net)**

Orphanet is an online database of rare diseases and related services provided throughout Europe. It contains information on over 5,000 conditions, including Williams Syndrome, and lists specialised clinics, diagnostic tests, patient organisations, research projects, clinical trials and patient registries relating specifically to Noonan Syndrome.

- **Department of Health—Personalisation (www.dh.gov.uk/en/SocialCare/Socialcarereform/Personalisation/index.htm)**

This website contains information on how the delivery of social care is being 'personalised'. This new approach uses individual budgets and direct payments to allow individuals more choice and control over the support they receive.

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