

Working for best care for people with Noonan syndrome

Dr Emma Burkitt Wright
Dr Sarah Wilson

Noonan syndrome
may affect 1 in 2000
people

- Feeding problems
- Pulmonary stenosis and other CHD; HCM
- Short stature
- Curly hair, ptosis, blue eyes, posteriorly rotated ears
- Undescended testes
- Learning and behavioural differences
- Lymphatic problems
- Bleeding/bruising
- Other rare complications

Noonan syndrome is very variable

- Whilst short stature is common, many have normal height
- Whilst congenital heart disease is common, many have no heart differences
- Some people's features of Noonan syndrome will appear before birth
- Others will only be diagnosed when another family member is diagnosed

Dyscerne Guidelines

https://rasopathiesnet.org/wp-content/uploads/2014/01/265_Noonan_Guidelines.pdf

Noonan Syndrome Clinical Management Guidelines

Management of Noonan Syndrome

A Clinical Guideline

Noonan Syndrome Guideline Development Group

The logo for dyscerne, featuring the text "A network of centres of expertise" in small blue font above "dyscerne" in large orange font, with "for dysmorphology" in small blue font below. A blue circular graphic with a white dot is to the left.

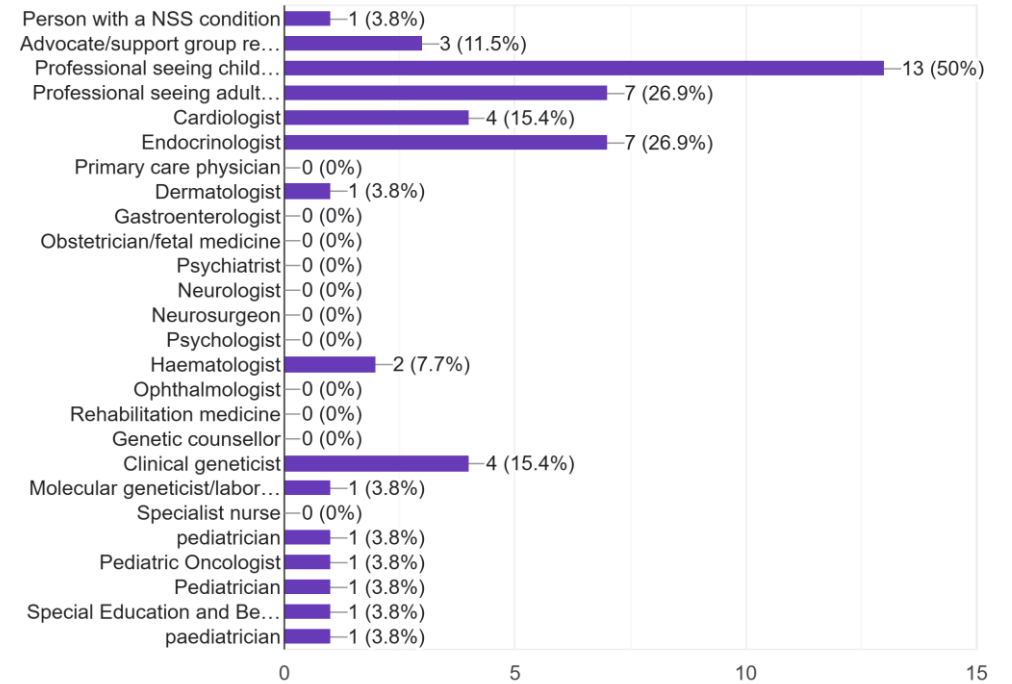
The logo for nowgen, with "nowgen" in large blue font and "A Centre for Genetics in Healthcare" in smaller blue font below. To the right is a vertical bar with red and orange segments.

gement Guidelines

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Consensus Management Guidance Consortium



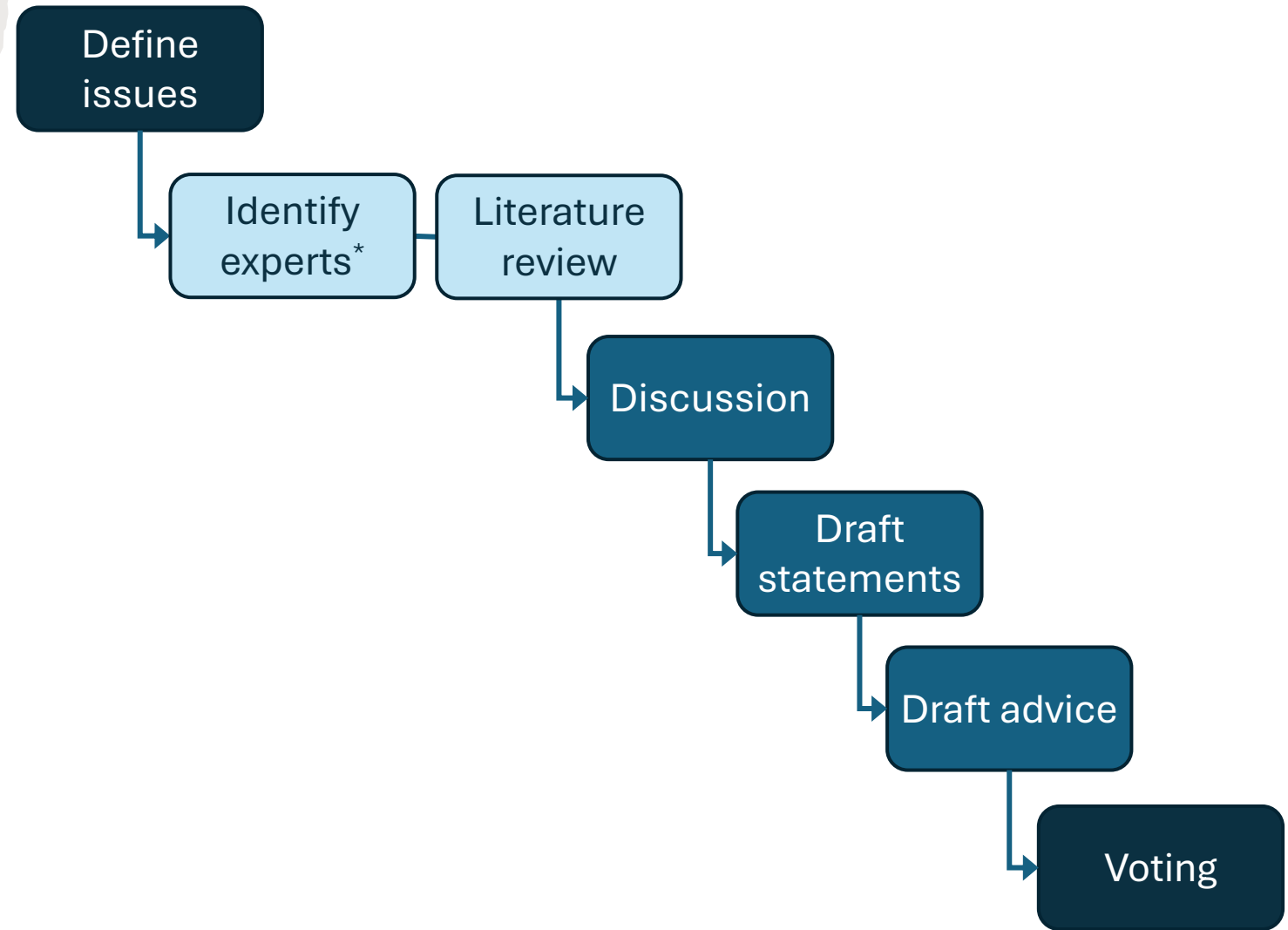
Aims of the revised guidance

- Practical and useful
- Generalist- and family-friendly
- Applicable across as broad a range of settings as possible
 - Multiple countries
 - All stages of life
 - All degrees of severity
 - All aspects of medical care
 - Non-medical aspects

What's included?

[illegible]

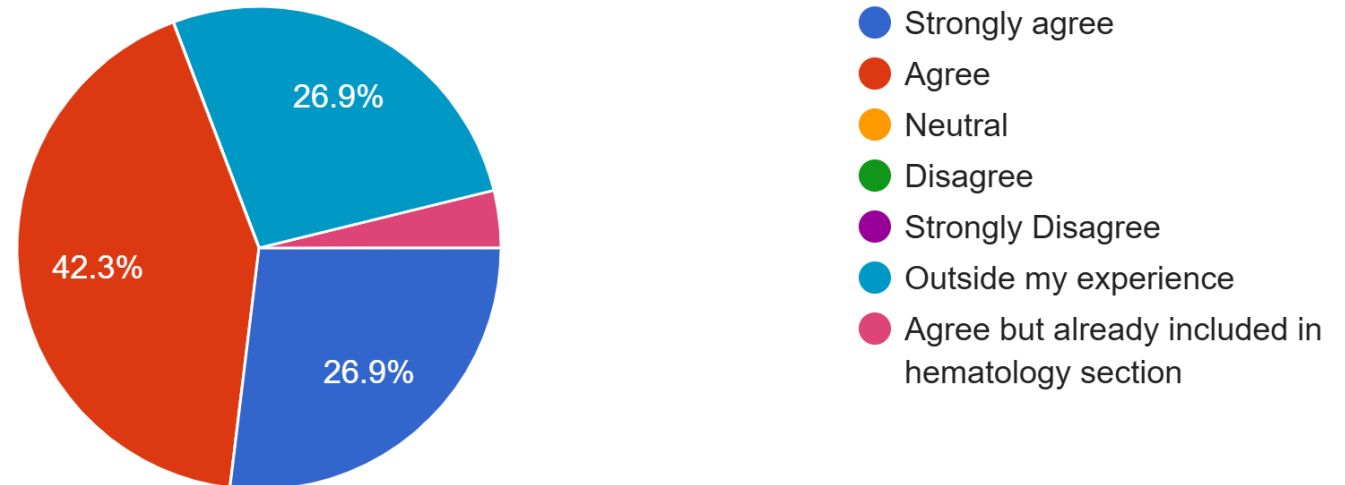
Delphi process



**professional and those with lived experience*

Example: Level of agreement

Menorrhagia (heavy periods) is common and may benefit from standard therapies such as tranexamic acid, or the use of oral contraceptives



Challenges



Remote working in large groups



Differences between healthcare systems

Differences in criteria for investigation and intervention

Differences in healthcare provision

Lead clinicians for adults

Some scientists work in semi-clinical roles in other countries



Levels of agreement



Working to timelines and competing pressures



HOSPITAL ROTHSCHILD APHP

		Proportion voting in favour (n in active disagreement)
Nosology		
1.1 The scope of this guidance includes NS, NSML, NSLH, NSLL, and CFCS, which share genetic, biochemical and clinical hallmarks. Detailed nosological discussion is beyond the scope of the current consensus document, but the genes implicated and clinical presentations for which the current guidance is intended are summarised in Table 1.		18/19
1.2 Whilst NSSD show considerable clinical overlaps with other RASopathies such as Costello syndrome, neurofibromatosis type 1 and Legius syndrome, each of those conditions are molecularly distinct from the NSSD. Costello syndrome and NF1 have existing well established clinical management guidance for the specific features of these conditions, including the high tumour risks, that are distinct from what is observed across the Noonan syndrome spectrum per se.		19/20
1.3 This consensus document is not intended to guide management of conditions other than those listed in Table 1. However, there may be rare individuals with specific variants in <i>HRAS</i> or <i>NF1</i> (for example) for whom NSSD management guidance (or elements of this) may be relevant, particularly those with very rare, less severe variants in <i>HRAS</i> who do not have core clinical features consistent with a diagnosis of Costello syndrome.		Unanimous
1.4.1 Incidence/prevalence estimates for NSSD are not based on validated epidemiological data. Available evidence supports a prevalence of 1:2,000-1:3,000 for NS. NSML, NSLH, NSLL, and CFCS are much rarer, probably		19/20

Nosology and diagnosis



Around 90% of people with Noonan syndrome can now have a gene change identified on testing



Knowing the exact gene change can guide care



Variability

Cardiology

- Congenital heart disease
- Hypertrophic cardiomyopathy
 - *RAF1*, *RIT1* higher risk
- Arrhythmia
 - Increased risk for arrhythmia with *RAF1* variants
- Detailed age-based surveillance schedule (infancy → adult)
 - According to initial findings
- Targeted therapies (MEK inhibitors) for severe HCM
- Guidance on GH and cardiac monitoring



Lymphatic



New dedicated section



Highlighting central conducting lymphatic anomalies



Genotype association (RIT1, SOS2)



Advanced imaging (MR lymphangiography)



Targeted medical/surgical interventions

Propanolol
MEK inhibitor
Embolisation
Surgical intervention

Endocrine

- Importance of measuring growth
 - Limitations of NS-specific growth charts
- Role of growth hormone
 - Growth hormone deficiency- clear benefit
 - Short stature in NS- individual consideration
 - Earlier GH initiation (from 4 years) suggested
- Genotype
- Monitoring protocols
 - IGF-1, metabolic screening, cardiac review
- Adolescence and adulthood
 - Delayed puberty
 - Gonadal function
 - Fertility



Musculoskeletal

- Check for scoliosis
- Physiotherapy and occupational therapy
 - For those with/at risk of joint contractures
 - Particularly in *MAP2K1*-associated CFC
 - Hyperextensibility
 - Joint pain
 - Muscle weakness
- Bone density
 - No extra checks needed
 - unless fragility fractures/known risk factors





Neurology and Psychology



Check developmental progress

Educational support



Awareness

ADHD/autism management pathways

Mental health surveillance (mood, alexithymia)

Genotype-specific epilepsy risk (e.g. BRAF)



Whether to do an MRI?

Low threshold for investigation

Baseline MRI in CFC

Feeding and GI

- Functional and motility disorders
- ARFID concept
- Tube feeding in prolonged/severe feeding difficulties
- Correlations
 - CFC- severe feeding disorders
 - *SHOC2/KRAS* may be associated with especially low BMI
- Consider ondansetron for refractory vomiting/food refusal
- ENT contribution

Skin

- Many different features
 - Especially for CFC
 - Skin care as for the general population
- Melanoma risk: low but awareness needed
 - Sun protection
 - Not smoking



Tumour risk

- Overall low tumour risk
 - No routine screening needed
 - Awareness to report new symptoms
- Genotype-risk awareness
 - JMML-focused surveillance in infancy (CBL)

Bleeding disorders

- Many people have easy bruising
 - Platelet dysfunction appears the commonest cause
- Specialist coagulation tests are possible
 - Before surgery
 - Where concerns about bleeding/easy bruising
 - For females after puberty
 - To inform management for heavy menstrual bleeding and future pregnancies



Sight and hearing



Baseline assessment, ongoing follow-up dictated by initial findings



CFC-specific issues- vision



Follow-up based on findings

General and Transition

- Transition planning
- Adult care continuity
- Fertility and genetic counselling
- Social independence & capacity

Adult NSSD (Noonan Spectrum Disorders) – Structured Clinic Checklist

1. Baseline

- ☐ Genetic diagnosis confirmed (if available)
- ☐ Genotype documented
- ☐ Transition summary reviewed

2. Cardiac

- ☐ Baseline echocardiogram + ECG completed
- ☐ If normal + asymptomatic → no routine follow-up
- ☐ Cardiology follow-up if: HCM, structural disease, arrhythmia, prior pathway inhibitor
- ☐ Screen for: chest pain, syncope, palpitations, reduced exercise tolerance

3. Bleeding / Coagulation

- ☐ Ask about easy bruising or bleeding
- ☐ If positive or pre-op → PT/APTT/platelets ± further testing
- ☐ Avoid NSAIDs if bleeding tendency
- ☐ Haematology plan before procedures if needed

4. Tumour Risk

- ☐ No routine screening required
- ☐ Investigate if symptomatic

5. Endocrine & Fertility

- ☐ GH therapy discontinued after growth completion
- ☐ Counsel regarding infertility risk (especially males)
- ☐ Offer fertility referral if required
- ☐ Check thyroid if clinically indicated

6. Mental Health & Neurodevelopment

- ☐ Screen for low mood, anxiety, emotional regulation issues
- ☐ Ongoing ADHD/autism support if relevant

7. Vision & Hearing

- ☐ Review only if symptomatic

8. Nutrition & GI

Prenatal

- Entirely new structured section:
 - Prenatal ultrasound findings
 - Genetic testing pathways
 - Fetal interventions
 - Pregnancy management for affected mothers



Features of new NSSD guidance

- Single disorder → spectrum (NSSD)
- Genotype-informed care
- Proactive risk stratification
- Full lifespan including prenatal
- Treatment prospects



Patient and family support organisations have been key to this work

