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Multidisciplinary Treatment of Patients With Noonan Syndrome
A Consensus Statement

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Abstract

IMPORTANCE Noonan syndrome (NS) is a rare developmental disorder and the most common condition among the RASopathies. Diagnosis and treatment of NS can be challenging due to the wide phenotypic variability of its manifestations. A multidisciplinary approach is essential, with continuous care required from infancy through adulthood; however, there is a lack of updated and widely shared guidelines for treating this condition.

OBJECTIVE To develop consensus statements on the diagnosis of NS, patient transition from pediatric to adult care, follow-up, and treatment of short stature with recombinant human growth hormone (rhGH).

EVIDENCE REVIEW Consensus was achieved through a modified Delphi process involving a multidisciplinary steering committee comprising 3 pediatric endocrinologists, 1 pediatric cardiologist, 1 molecular geneticist, along with a 25-member expert panel who had expertise in treating NS at clinical reference centers in Italy. In December 2023, the steering committee drafted 47 statements based on published evidence and clinical experience. These statements were then submitted to the expert panel, which provided anonymous feedback on their level of agreement or disagreement between January and March 2024.

FINDINGS All 25 members of the expert panel completed the Delphi survey and consensus was achieved on all statements after the first round of voting. Full agreement (100%) was reached on several key points: importance of molecular characterization for diagnosis, prognosis, and treatment decisions; necessity of a multidisciplinary approach to NS treatment; need for improved transition from pediatric to adult care; increased risk in patients with hypertrophic cardiomyopathy (HCM); importance of monitoring adherence to rhGH therapy; acknowledgment that partial GH insensitivity should not exclude rhGH therapy; and safety concerns regarding rhGH therapy, particularly related to HCM and the risk of malignant neoplasms.

CONCLUSIONS AND RELEVANCE Effective treatment of NS requires a multidisciplinary and personalized approach from infancy through adulthood. This comprehensive set of consensus statements is intended for clinicians to implement more effective care of patients with NS.

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Introduction

Noonan syndrome (NS) is a clinically variable and genetically heterogeneous developmental disorder characterized by distinctive facial features, postnatal short stature, and cardiac defects.[1-3] Additional characteristics include endocrine abnormalities, cryptorchidism, delayed puberty, chest malformations, bleeding disorders, and neurocognitive or behavioral issues.[3,4] NS is primarily inherited as an autosomal dominant trait, although recessive forms have recently been identified.[5-7] A substantial proportion of NS cases arise from de novo germline variants.[8]

Ras/mitogen-activated protein kinase (RAS-MAPK) aberrant activation causes NS by disrupting cell responses to growth factors, hormones, and cytokines.[9] Gain-of-function variants in *PTPN11*, encoding a positive modulator of RAS proteins, occur in approximately 50% of affected individuals.[10,11] Variants in other RAS-MAPK pathway genes (eg, *SOS1*, *NRAS*, *KRAS*, *RAF1*, and *BRAF*, among others) account for the remaining cases.[11] Notably, hyperactivated RAS-MAPK signaling also underlies other developmental disorders associated with NS, termed RASopathies.[12,13]

The multisystem nature and phenotypic variability of NS necessitate lifelong, multidisciplinary care from infancy through adulthood.[14,15] This care requires a multidisciplinary team with expertise in treating congenital and evolving cardiac conditions, endocrine dysfunction, short stature, and other medical problems.[3] Multidisciplinary care facilitates early identification and complications treatment, improves developmental milestones, and reduces long-term health care burden.[16] Studies show that structured care teams addressing cardiac, feeding, neurodevelopmental, and endocrine needs can improve quality of life (QoL) and long-term outcomes.[17]

Although comprehensive system-specific guidelines for NS exist, the absence of an updated, integrated framework for multidisciplinary treatment from fetal life through adulthood continues to be a substantial gap in the literature.[2,18-20] In response, this study proposes a practical guide for coordinated, lifelong care that promotes specialist collaboration to improve outcomes across the developmental continuum in individuals with NS.

Based on these considerations, a multidisciplinary team of NS experts from Italian reference centers developed consensus statements on diagnosis, transition, follow-up, and recombinant human growth hormone (rhGH) treatment for short stature. This study presents the outcomes of this collaborative effort.

Methods

This consensus statement was developed using a modified Delphi process following the Accurate Consensus Reporting Document (ACCORD) framework,[21,22] ensuring methodological rigor while adapting to experts' limited availability. To ensure timely expert input and efficient consensus-building, the process consisted of a single-round evaluation of predefined statements, followed by structured group discussions. Consensus was reached in the first round, reflecting strong initial agreement. This format preserved key Delphi features, while adapting to clinical and logistical needs. While ethical review requirements vary by context, this project followed the approach of other consensus studies registered as service improvement initiatives involving health care professionals in their professional roles.[23] The study protocol did not require research ethics board approval, and it was not registered with any clinical trial or research registry. Members of the public, patients, and carers, whose involvement is increasingly recognized in NS research and guideline development,[24] were not included in the study's consensus process.

Most panelists belong to the Italian Multidisciplinary Noonan Syndrome Working Group of the Italian Society of Pediatric Endocrinology and Diabetology. The group developed consensus statements and guidelines tailored to the needs and resources of the Italian health care system for treating NS. No organizational endorsement or sponsorship was requested or obtained for this Delphi consensus.

A multidisciplinary steering committee was selected to ensure balanced expertise, clinical experience, and scientific authority in the field. Members were chosen for their role as opinion leaders, active participation in relevant studies and guidelines, and their ability to represent diverse clinical and institutional areas, ensuring an integrated and comprehensive approach to the topics addressed.

Similarly, the expert panel was selected by the steering committee to represent professionals qualified to address the study topics. Panelists received individual email invitations from the steering committee detailing the study's objectives, methods, and time requirements. They were encouraged to suggest qualified individuals through a snowball sampling approach. Follow-up communications and reminders were managed to ensure consistency and effective response tracking. An honorarium was provided to panelists, following institutional policies and ethical standards.

The facilitator, experienced in Delphi methods and without conflicts of interest, moderated the discussions, supported communication, coordinated group interactions, and ensured adherence to methodological procedures and process integrity. The facilitator was not part of the steering committee, and, under the facilitator's guidance, the committee defined the study objectives, developed the initial statements, selected the expert panel, and supervised the process. Finally, consensus was defined a priori as 70% agreement or greater, in line with thresholds adopted in similar studies.[25]

The modified Delphi process consisted of 4 steps (**Figure**). In September 2023, the steering committee met virtually to identify priority areas in NS treatment for discussion and update, based on literature review and clinical experience (step 1). Four areas were identified (diagnosis, transition from pediatric to adult care, follow-up, and treatment with rhGH). Within these areas, 17 items needed to be specifically addressed (October 2023); these included (1) clinical diagnosis, (2) genetic or molecular diagnosis, (3) prenatal diagnosis, (4) genetic counseling and genotype-phenotype correlations, (5) treatment, (6) critical issues of the transition, (7) pubertal function and fertility, (8) orthopedic or skeletal problems, (9) oncologic issues, (10) endocrine issues, (11) coagulation issues, (12) cognitive and behavioral issues, (13) cardiologic issues, (14) criteria of eligibility for rhGH therapy, (15) evaluation of the efficacy of rhGH therapy, (16) monitoring of rhGH therapy, and (17) evaluation of the safety of rhGH therapy. Between August 8 and August 13, 2023, a literature search was conducted using PubMed and Web of Science. Studies were eligible for inclusion if they were original research articles, systematic or narrative reviews, expert consensus statements, were peer-reviewed, written in English, available in full-text, and relevant to the topic. Studies were excluded if they lacked reporting of objectives and conclusions, were limited to abstracts, case reports, theses, non–peer-reviewed conference proceedings or were inaccessible in full text. The panel received the

Figure. Flowchart Illustrating the Consensus Finding Process

GH indicates growth hormone; NS, Noonan syndrome; rhGH, recombinant human growth hormone.

supporting literature for each statement before voting. Quality of evidence was rated using a modified scheme from the Oxford Centre of Evidence-Based Medicine.[26]

The steering committee generated 47 statements (step 2), which were discussed and finalized during a virtual meeting in December 2023. The statements were submitted to the expert panel who rated their level of agreement on each statement using a 9-point Likert scale (step 3; January to March 2024), which yields more statements being rated as critical compared with 3-point scales.[27]

The panel members were identified based on their expertise in the diagnosis and treatment of NS and RASopathies. Overall, 25 clinicians (15 pediatricians, 6 pediatric endocrinologists, 3 cardiologists, and 1 geneticist) were invited. This number was selected to balance a range of perspectives with manageable group dynamics for consensus-building. This sample size is consistent with previous health care quality and safety studies that reported stable results using panels of 23 experts.[28] Moreover, evidence suggests that stability improves with panels of 20 or more participants.[29]

Following the Delphi method,[21] the steering committee, which did not have voting rights, oversaw the study, developed and refined the questionnaire, and defined consensus criteria. The expert panel was responsible for voting and achieving consensus on the statements. Voting was anonymous, performed online, and comments were optional.

In May 2024, the steering committee met virtually to discuss the survey results (step 4). All statements achieved consensus (median score ≥7) after the first round of voting, so no further rounds were needed.

Results

The Delphi survey achieved a 100% response rate (ie, all 25 invited participants), and generated 47 statements, with written comments provided for most statements (41 statements [87%]), and 26 statements (55%) reaching agreement exceeding 95%. Full consensus (100% agreement) was established on importance of the molecular characterization for confirming the diagnosis and guiding patient care (statements 3, 21, and 31); necessity for a multidisciplinary approach to NS treatment (statement 12); need for improving care during transition (statements 14 and 15); increased risk of hypertrophic cardiomyopathy (HCM) in NS (statement 30); rhGH therapy administration in presence of reduced response to GH (statement 36); importance of monitoring adherence to rhGH therapy, particularly during dose adjustments (statement 41); and need to address safety issues associated with rhGH therapy (statements 43, 45, and 47). Statements 29 and 37 achieved consensus levels of 72% (18 of 25 participants) and 76% (19 of 25 participants), respectively.

Diagnosis (Statements 1-10)

Table 1 shows consensus statements regarding diagnosis of NS. Early diagnosis of NS is essential for timely referral to appropriate care.[4] Awareness and knowledge of NS and RASopathies must improve among pediatricians, general practitioners, pediatric endocrinologists, cardiologists, and prenatal care professionals.[30] Prompt molecular characterization is essential to confirm NS diagnosis, differentiate it from other RASopathies and developmental disorders, optimize patient care, and improve genetic counseling.[2,18] Because NS is genetically heterogeneous,[7] molecular analysis using gene panels including all known RASopathy-related genes should be performed when patients present with NS manifestations. When the clinical presentation is unclear, whole-exome or clinical-exome sequencing is recommended.

Prenatal molecular analysis is highly recommended in cases of familial occurrence. Additionally, prenatal genetic testing should be considered when a cardiac defect accompanies ultrasonography findings.[31-33] Cardiac findings should be confirmed postnatally, and if confirmed, prompt genetic counseling and comprehensive clinical evaluation. Genetic testing is recommended, even in clinically confirmed NS because it associates specific variants with disease features and rhGH treatment responses. While genotype-phenotype correlations have been established (statement 10),[2,3,8,20] further research is needed to identify and validate putative correlations involving recently identified NS genes.

Transition (Statements 11-18)

Table 2 shows statements regarding the transition from pediatric to adult care for patients with NS. Although NS natural history, particularly in adults, is not well understood,[3,34,35] there is consensus on the need for regular adulthood follow-up to treat its complications.[3,15,20] Several authors have proposed age-based follow-up guidelines beyond pediatric care[3,4,14,18]; however, the optimal approach to transitioning from pediatric to adult care remains unclear. The European Medical Education Initiative survey on NS highlighted an urgent need for health care professionals trained to treat this phase.[18] Similarly, pubertal delay and fertility issues require attention during transition to ensure timely intervention and support for normal adult fertility (statements 16-18).[14,36,37]

Follow-Up (Statements 19-31)

Table 3 shows statements on follow-up for patients with NS. Orthopedic and skeletal problems (statements 19-20), increased risk of developing malignant neoplasms (statements 21-22), endocrine dysfunction (statement 23), coagulation problems (statement 24), cognitive impairment and behavioral issues (statements 25-27), and heart disease (statements 28-31) require particular attention and regular follow-up for patients with NS. This list is not exhaustive and does not exclude other clinical features, such as feeding problems and lymphedema.[2-4,14,30,38]

Feeding difficulties are common in infants with NS, and approximately 20% of individuals affected develop lymphedema.[4,14,30,38] These children require multidisciplinary nutrition monitoring,[39] lymphatic status, and growth trajectories, particularly if pathogenic variants are present.[39-41] Ocular, auditory, and dermatological manifestations should also be assessed and

Table 1. Consensus Statements on Aspects Related to the Diagnosis of Patients With Noonan Syndrome

Statement	Score, median	Level of agreement, No. (%) (N = 25)	Quality of evidence[a]
Clinical diagnosis of NS or RASopathies			
1. To promote early diagnosis, it is essential to improve the knowledge of NS among local health care practitioners of reference (eg, pediatricians and general practitioners)	9	23 (92)	4
2. Knowledge of RASopathies is a priority in the context of prenatal diagnosis to ensure early identification and treatment of the condition.	9	24 (96)	4
Genetic or molecular diagnosis			
3. Molecular confirmation is essential for effective patient treatment and proper genetic counseling.	9	25 (100)	2
4. In cases of clinical diagnosis provided with high confidence, clinicians should request molecular analyses that use an updated panel of genes associated with RASopathies; in cases of a suspicious and/or uncertain clinical picture, they should request exome sequencing or clinical exome sequencing.	9	23 (92)	3
5. A gene panel including all genes associated with RASopathies should be considered in cases of short stature with a suggestive syndromic clinical picture.	9	24 (96)	3
Prenatal diagnosis			
6. Prenatal diagnosis performed on fetal DNA, either circulating or extracted from chorionic villi or amniocytes, is indicated if one of the parents is affected by an RASopathy.	8	20 (80)	3
7. In cases where there is a fetal ultrasonography suspicion of hypertrophic cardiomyopathy or supravalvular pulmonary valve stenosis associated with valve dysplasia, the possible association with NS should be kept in mind to ensure referral of the parents to prenatal genetic counseling and, subsequently, of the infant to postnatal clinical genetic examination.	9	24 (96)	4
8. Prenatal variant analysis of the entire panel of known genes associated with RASopathies should be performed in cases of significant ultrasonography features (eg, presence of cystic hygroma, ascites, fetal hydrops, or polyhydramnios), isolated or associated with other suggestive fetal features (eg, heart disease).	9	23 (92)	4
Genetic counseling and genotype or phenotype correlations			
9. Prompt molecular analysis and identification of the involved gene and pathogenic variants can facilitate better care of the newborn in terms of both survival and overall health or quality of life. Moreover, it can be an informative tool for the genetic counseling of the family.	9	24 (96)	3
10. Several clinically relevant genotype-phenotype associations (eg, presence of hypertrophic cardiomyopathy with *RAF1*, *RIT1*, and *LZTR1* variants; improved cognitive status with *SOS1* variants; and good stature growth with *SOS1* variants) make molecular characteristics (ie, involved gene and type of variant) a highly informative and useful tool for optimizing patient care.	9	24 (96)	3

Abbreviation: NS, Noonan syndrome.

[a] Quality rating scheme (modified from the Oxford Centre of Evidence-Based Medicine).[26] A rating of 1 indicates properly powered and conducted randomized clinical trial or systematic review with meta-analysis; 2, well-designed controlled trial without randomization or prospective comparative cohort trial; 3, case-control studies or retrospective cohort study; 4, case series with or without intervention or cross-sectional study; 5, opinion of respected authorities or case reports.

treated to optimize developmental outcomes and QoL.[2,42-44] Endocrine issues are an important aspect of NS[14,36]; therefore, regular evaluation of growth and gonadal function is recommended.[45]

Cardiac issues include congenital heart disease and HCM,[46] with pulmonary valve stenosis being the most common. While isolated pulmonary valve stenosis is usually treated with balloon angioplasty,[47] patients with NS often present leaflet dysplasia or supravalvular stenosis (statements 29-30), for which surgery yields better long-term outcomes.[48] Preprocedural echocardiography helps distinguish isolated valve stenosis from other lesions, guiding appropriate treatment. Statement 29, with 72% agreement (18 of 25 participants), may reflect preference for noninvasive treatment despite a lack of supporting evidence.

Molecular profiling identifies patients who may develop late-onset HCM.[49,50] Concomitant NS and HCM in younger patients may increase the risk of sudden cardiac death. This risk is even higher in patients with Noonan-like or Costello syndrome and HCM, indicating a poorer long-term prognosis.[51] Therefore, regular follow-up is recommended.

Skeletal abnormalities associated with NS can be surgically corrected.[9,52,53] However, due to comorbidities and coagulation problems,[54] bleeding diathesis is recommended before intervention to reduce bleeding risk (statement 24).[55] Multidisciplinary care is strongly recommended for major surgeries (statements 19 and 20).

RAS-MAPK pathway dysregulation in pediatric patients increases the incidence of hematologic malignant neoplasms and solid tumors.[56] While recommendations address the risk of hematologic malignant neoplasms in early childhood, no consensus exists on monitoring strategies for solid tumors in this phase.[56] Pathogenic variants of *PTPN11* and *KRAS* are associated with tumor predisposition,[56] while the risk associated with other genes (eg, *SOS1*, *LZTR1*, *RIT1*, *NRAS*, *MRAS*, and *RRAS2*) is poorly characterized. Pathogenic variants should be evaluated to determine oncologic risk, and cancer surveillance is recommended (statements 21 and 22). Although recommendations suggested surveillance only for patients with higher-risk germline pathogenic variants,[57,58] a 2024 update[58] emphasizes the importance of early and regular monitoring for all individuals with NS and

Table 2. Consensus Statements on Aspects Related to Transition From Pediatric to Adult Care of Patients With Noonan Syndrome

Statement	Score, median	Level of agreement, No. (%) (N = 25)	Quality of evidence[a]
Treatment			
11. Given the significant genetic heterogeneity and marked genotypic and phenotypic variability of NS, each patient requires individualized treatment and may have a natural history distinct from that of other patients, which should be considered when the pathway of care is started.	9	24 (96)	4
12. A specific multidisciplinary approach by adequately trained health care professionals can provide appropriate care to patients with NS.	9	25 (100)	4
Critical issues of the transition			
13. Despite the limited knowledge of the natural history of NS, clinical problems in adulthood include evolving cardiac aspects (related to hypertrophic heart disease, in particular) and problems related to orthopedic, endocrine-metabolic, coagulation, fertility, cognitive-behavioral, and psychological issues. Thus, specialists treating adult patients should also receive appropriate training.	9	24 (96)	3
14. The figure of the case-manager or general practitioner is crucial for the transition phase to treat the preexisting and evolving aspects of NS.	9	25 (100)	5
15. The transition from adolescent to adult can be a particularly vulnerable time. An educational approach to the transition phase is essential (for taking charge of the transitioning patient and counseling about reproductive health).	9	25 (100)	5
Pubertal function and fertility			
16. In females and, more frequently, in males, puberty is delayed. However, gonadal dysfunction, hypogonadism, and possible discrepancies between gonadal volume and gonadal function must be excluded.	9	24 (96)	4
17. In patients with a history of cryptorchidism, testicular function should be evaluated with targeted examinations.	9	22 (88)	3
18. Fertility problems should be considered at peripubertal age to implement all preventive measures required for normal fertility in adulthood.	9	23 (92)	4

Abbreviation: NS, Noonan syndrome.

[a] Quality rating scheme (modified from the Oxford Centre of Evidence-Based Medicine).[26] A rating of 1 indicates properly powered and conducted randomized clinical trial or systematic review with meta-analysis; 2, well-designed controlled trial without randomization or prospective comparative cohort trial; 3, case-control studies or retrospective cohort study; 4, case series with or without intervention or cross-sectional study; 5, opinion of respected authorities or case reports.

Table 3. Consensus Statements on Aspects Related to the Follow-Up and Treatment of Patients With Noonan Syndrome

Statement	Score, median	Level of agreement, No. (%) (N = 25)	Quality of evidence[a]
Follow-up			
Orthopedic and skeletal problems			
19. Given the possible and relevant comorbidities associated with NS (eg, cardiopathy, coagulopathy, and central nervous system abnormalities, among others), the importance of a specialized multidisciplinary team should be considered in the correction of scoliosis-kyphosis and chest abnormalities.	9	23 (92)	4
20. Chest abnormalities require specialists able to correct pectus excavatum with the assistance of a cardiac surgeon when major cardiomyopathies coexist.	8	22 (88)	3
Oncologic issues			
21. Pathogenic variants should be carefully evaluated to determine the possible risk of cancer.	9	25 (100)	3
22. Clinical (eg, evaluation of nevi), biochemical (regular performance of blood tests or specific tumor markers), and radiologic (ultrasonography, MRI, and CT-PET scans) preventive measures should be considered (and possibly implemented) in each patient with NS, taking into account the specific variant and its risk.	9	23 (92)	3
Endocrine issues			
23. In every patient with NS, the endocrine system should be regularly examined for aspects of growth and gonadal function and/or auxologic characteristics.	9	24 (96)	4
Coagulation issues			
24. Because patients with NS have problems of coagulation and platelet function, the study of bleeding diathesis is recommended before surgery.	9	23 (92)	4
Cognitive and behavioral issues			
25. Each patient with NS should be evaluated for any cognitive, behavioral, psychological, and/or neuropsychiatric issues.	9	23 (92)	4
26. Given the frequency and clinical implications of neuropsychological and behavioral issues, most children may need rehabilitation support (eg, physiotherapy, psychomotricity, and speech therapy), although the overall prognosis is good.	8	22 (88)	4
27. Because patients with NS present with alexithymia, social maladjustment, low self-esteem, and, in some cases, variable cognitive impairment, psychological support aimed at both patients and their families should always be implemented.	8	24 (96)	4
Cardiologic issues			
28. Although the characteristic cardiac defects of NS are pulmonary valve stenosis, which presents as supravalvular pulmonary valve stenosis associated with valve dysplasia, and isolated hypertrophic, obstructive, or nonobstructive left ventricular or biventricular cardiomyopathy, other congenital cardiac defects may be present, even in the absence of the former.	9	24 (96)	4
29. Supravalvular pulmonary valve stenosis should be treated with surgery, given the lack of efficacy of percutaneous treatments.	9	18 (72)	3
30. Patients with NS-associated hypertrophic cardiomyopathy have a higher risk profile and a lower life expectancy, particularly if the onset with decompensation occurred before 6 mos of age, based on the specific genetic profile (eg, *RAF1* variants).	8	25 (100)	3
31. In the presence of a specific genetic profile (eg, variants of *LZTR1* or *RIT1*) and/or electrocardiographic abnormalities, careful cardiologic follow-up is recommended to detect the possible presence of late-onset hypertrophic cardiomyopathy.	9	25 (100)	3
Therapy with rhGH			
Criteria for the selection of patients eligible for GH therapy			
32. The proper selection of patients eligible for rhGH therapy requires auxologic (height, growth velocity, sitting height, and head circumference), biochemical (glucose metabolism, lipid metabolism, coagulation, and thyroid metabolism), and radiologic assessments (to exclude hypothalamic-pituitary, cerebral, or vascular malformations).	9	24 (96)	3
33. Based on auxologic, biochemical, and radiologic features, in some cases, it may be important to consider the assessment of pituitary function to best adjust therapy in patients with GHD.	9	21 (84)	3
34. In patients with auxologic clinical features suggestive of GHD, evaluation with GH stimulation test may be indicated.	9	22 (88)	4
35. RhGH therapy should be introduced only after detailed echocardiographic evaluation, particularly in patients carrying specific gene variants (eg, *RAF1*, *LZTR1*, *RIT1*, or *MRAS*); in patients with hypertrophic cardiomyopathy, rhGH therapy is reserved only for patients with mild disease or mild to moderate disease without obstruction, in the absence of major evidence of evolving disease.	9	23 (92)	3
36. The presence of varying degrees of GH insensitivity in patients with NS should not be a barrier to the start of personalized rhGH therapy.	9	25 (100)	3
37. In patients with NS and a history of inactive malignant neoplasms, with confirmed secondary hypopituitarism, there is no contraindication to rhGH therapy as per international indications for cancer survivors.	8	19 (76)	4
Evaluation of the efficacy of GH therapy			
38. Most data on response to rhGH treatment come from uncontrolled observational studies, often involving small numbers of patients, the majority of whom were molecularly uncharacterized and different in terms of age at therapy start, rhGH dosage, and treatment duration. This, along with the lack of genotype-phenotype correlation, is a limitation in the prediction and interpretation of the results.	9	23 (92)	4
39. Auxologic data play a key role and are indicative of the efficacy of therapy, also in relation to the different prescribable doses.	9	24 (96)	3

(continued)

Table 3. Consensus Statements on Aspects Related to the Follow-Up and Treatment of Patients With Noonan Syndrome (continued)

Statement	Score, median	Level of agreement, No. (%) (N = 25)	Quality of evidence[a]
Monitoring of rhGH therapy			
40. Monitoring of therapy should be based primarily on growth velocity and response to treatment.	9	23 (92)	4
41. Given that the association of rhGH therapy with growth decreases over time, if the dose of rhGH is increased, it is recommended to monitor IGF-1 SD scores during dose increase.	9	25 (100)	3
42. Because NS may be characterized by resistance to GH or IGF-1, evaluation of treatment adherence is recommended.	9	24 (96)	4
Evaluation of the safety of GH therapy			
43. In rhGH therapy, the safety aspects to be considered most carefully are those related to possible hypertrophic cardiomyopathy (evidence of increased ventricular thickness) and possible occurrence of neoplasia; adequate counseling of parents and/or patients is recommended.	9	25 (100)	3
44. Because patients with NS have an increased risk of developing certain malignant neoplasms, increased surveillance of the most frequently involved sites is recommended during the follow-up of patient treated with rhGH.	9	21 (84)	3
45. It is recommended that IGF-1 SD score values be kept within the safety levels adopted in clinical practice.	9	25 (100)	3
46. Brain MRI is recommended before starting rhGH therapy.	9	23 (92)	3
47. The use of specific registries, especially if detailed genetic characterization is available, may be crucial for resolving many issues related to treatment safety.	9	25 (100)	3

Abbreviations: CT-PET, computed tomography-positron emission tomography; GH, growth hormone; GHD, growth hormone deficiency; IGF-1, insulin-like growth factor-1; NS, Noonan syndrome; MRI, magnetic resonance imaging; rhGH, recombinant human growth hormone.

[a] Quality rating scheme (modified from the Oxford Centre of Evidence-Based Medicine).[26] A rating of 1 indicates properly powered and conducted randomized clinical trial or systematic review with meta-analysis; 2, well-designed controlled trial without randomization or prospective comparative cohort trial; 3, case-control studies or retrospective cohort study; 4, case series with or without intervention or cross-sectional study; 5, opinion of respected authorities or case reports.

related RASopathies, particularly during early childhood, focusing on hematologic symptoms, hepatosplenomegaly, and signs of solid tumors.

Patients with NS exhibit reduced cognitive performance, behavioral problems, and alexithymia.[35,59,60] Systematic assessment, along with educational and psychological support, is recommended for these individuals.[2,4,35]

RhGH Therapy (Statements 32-47)

Table 3 shows statements regarding treatment of patients with NS using rhGH therapy. Short stature affects 70% to 80% of patients with NS,[61,62] with slowed growth in the first year[63] and average height approaching the third percentile by the year's end. Height stabilizes between 2 and 4 years at −2 to −2.5 SDs and remains consistent through childhood.[63] Pubertal growth is delayed, beginning around age 13 to 14 years, with linear growth extending into the early twenties, resulting in adult height around −2 SDs.[63] The causes likely include GH deficiency (GHD), GH neurosecretory dysfunction, partial GH insensitivity (characterized by low insulin-like growth factor 1 [IGF-1] secretion despite normal or elevated GH levels), and poor IGF-1 response in target tissues.[64,65] Additionally, *BRAF* variants may cause endocrine deficiencies, including hypopituitarism.[66] Therefore, following GH deficiency diagnosis, performing magnetic resonance imaging of the hypothalamus and pituitary is advised to assess structural or neoplastic causes, and other central nervous system pathologies.[67]

In 2007, rhGH therapy was approved by the US Food and Drug Administration for the treatment of short stature associated with NS. In Italy, the treatment became available in May 2021. Eligibility for rhGH treatment (statements 32-37) should be determined based on auxologic parameters.[68] Biochemical assessments of glucose and lipid metabolism, coagulation, and thyroid metabolism are recommended because rhGH therapy can alter these processes.[68]

Therapy efficacy and safety have been assessed in several studies.[65,68] However, variations in protocols, outcome measures, and the absence of molecular profiling remain substantial limitations.[62,65] Pooled analyses, long-term cohorts, and reviews show rhGH increases first-year growth velocity,[14,62,65,68-70] with better outcomes associated with prepubertal initiation and longer treatment duration.[14,62,65,68-70] Moreover, the safety profile is deemed reassuring, with no major

adverse events reported.[14,62,65,68-70] However, due to the lack of prospective studies on long-term effects and benefits,[68,70,71] treatment efficacy should be evaluated using auxologic data (statement 39)[65,67] including population-based growth charts.[68,72,73]

IGF-1 values and growth velocity are crucial for monitoring rhGH therapy (statements 40-42).[67,68,70] Patients with NS often exhibit variable GH and IGF-1 resistance, leading to moderate responses to rhGH doses. Consequently, suboptimal adherence may reduce treatment efficacy and the benefits of dose increases.[74] A systematic review found that nonadherence to pediatric therapy in Italy ranged from 10% to 30%. Therefore, regular monitoring is strongly recommended to ensure effectiveness.[75] Registries for pediatric rhGH exist but are inconsistently used[20,65,76]; their development and use (ideally with genetic data) are encouraged to address evidence gaps.

If rhGH is unavailable, alternatives such as nutritional optimization, gonadotropin-releasing hormone analogs, aromatase inhibitors, and other investigational options should be individualized and used cautiously due to potential adverse effects. While rhGH therapy enhances linear growth in patients with NS,[77] concerns remain about worsening preexisting cardiac conditions.[78,79] Echocardiographic assessment is recommended in carriers of germline pathogenic variants associated with cardiac defects.[47] In patients carrying *RIT1* and *RAF1* variants, rhGH therapy before the age of 4 years may exacerbate HCM.[65] Therefore, close cardiac monitoring is recommended, and therapy should be discontinued at the early signs of HCM.[68] Partial GHI and a history of inactive malignant neoplasms, along with confirmed secondary hypopituitarism, do not contraindicate rhGH therapy (statement 37).[68,80-82] However, statement 37 received a moderate level of agreement (19 of 25 participants [76%]), likely due to concerns about the risk of malignant neoplasms associated with the therapy.

HCM and the risk of malignant neoplasms are safety concerns associated with rhGH therapy in patients with NS (statements 43 and 44).[2,46,57,68,83] Although well tolerated, this treatment requires cautious monitoring and individualized treatment plans in patients with certain genetic variants.[64,84,85] For these reasons, safety monitoring and informed discussion with families are strongly advised.[86] IGF-1 levels should remain within the limits of 2 SDs.[87] Moreover, magnetic resonance imaging is recommended before starting the therapy.

Discussion

This consensus statement was developed to guide clinicians, particularly pediatricians and general practitioners, in the multidisciplinary treatment of patients with NS from diagnosis to rhGH treatment, transition to adult care, and long-term follow-up. This initiative was driven by the need for updated and comprehensive recommendations for the NS treatment. These recommendations must be interpreted and adapted by clinicians following their local clinical infrastructure, resource availability, and patient population to ensure feasible implementation.

Experts' comments indicate that patient genotyping faces obstacles in many centers. Barriers include restricted access to advanced diagnostic tools and their associated costs. Additionally, limited awareness of fetal features of NS among obstetricians and gynecologists has been reported during prenatal ultrasonography analyses.[88] The transition from pediatric to adult care is also challenging and lacks organization in clinical practice.

Early diagnosis and multidisciplinary treatment are essential to improve health outcomes and enhance long-term development and QoL. Timely diagnosis enables targeted interventions, such as rhGH therapy, speech and occupational therapies, and regular cardiac evaluations.[16] Studies show that children with NS receiving early, coordinated care and diagnosis achieve key milestones sooner,[16] while comprehensive treatment reduces the frequency and duration of hospitalizations.[89] Initiating a multidisciplinary approach with early involvement of specialists, such as geneticists, cardiologists, endocrinologists, neurologists, and rehabilitation therapists, ensures coordinated, personalized care, improves clinicians-family communication, and enhances outcomes and QoL.

Italian guidelines indicate that rhGH therapy is reimbursable for patients with genetically confirmed NS and a height of −2.5 SDs or less[90] However, because many NS patients have a height between −2.0 and −2.5 SDs, current guidelines may restrict therapy access. In other countries, this therapy is approved for treating children with growth failure or short stature due to NS, without specific indications about height limits[91,92] or with less stringent limits (eg, France defines eligibility as height less than −2.0 SDs).[93]

Limitations

Although the panel was multidisciplinary, its composition was predominantly Italian, which may introduce bias and limit the international generalizability of the findings.[94] Moreover, structured feedback can carry the risk of promoting artificial consensus.[94]

Conclusions

NS is a rare congenital developmental disorder marked by genetic and clinical variability. Effective treatment requires a multidisciplinary and personalized approach spanning from infancy to adulthood. This set of consensus statements is expected to aid clinicians in the care of patients with NS.

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SUPPLEMENT.
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