Clinical Standards for GH Treatment of Growth Disorders in Childhood and Adolescence excluding GHD

This document has been developed by **the BSPED Growth Disorders Special Interest Group (SIG)** and collates existing eligibility criteria and published guidance for the licenced indications of GH treatment during childhood and adolescence excluding growth hormone deficiency.

Guidance for GH treatment of growth hormone deficiency (GHD) can be found here: https://www.bsped.org.uk/media/1980/clinical-standards-for-gh-treatment-of-ghd-in-childhood-and-adolescence.pdf

The aim of this document is to improve patient experience, standardise care and improve equity of access to specialist services and treatment.

This guidance covers clinical standards of rhGH therapy for the following:

1. Turner syndrome
2. Prader-Willi syndrome
3. Chronic renal insufficiency
4. Born small for gestational age with subsequent growth failure at 4 years of age or later
5. Short stature secondary to homeobox-containing gene (SHOX) deficiency
6. Noonan syndrome

Authors: HL Storr, M Ajzensztejn, R Dias, T Hulse, A Rice, P Sachdev, MG Shaikh, JH Davies

BSPED Growth Disorders SIG: Helen Storr (Chair), Justin Davies (Deputy), Michal Ajzensztejn, Karen Blair, Gary Butler, Simon Chapman, Jenny Child, Peter Clayton, Renuka Dias, Evelien Gevers, Rebekah Glen, Tony Hulse, Phillip Murray, Alan Rice, Pooja Sachdev, Senthil Senniappan, Jarod Wong.

Introduction

Somatropin (recombinant human growth hormone; rhGH) is licenced in the UK for the conditions 1-6 listed above. Somatotropin is also recommended and approved by NICE (1) for conditions 1-5. In 2019, Noonan syndrome was added to the approved UK licenced indications for somatropin (but is currently not NICE approved).

CLINICAL STANDARDS FOR CHILDREN AND ADOLESCENTS TREATED WITH RECOMBINANT HUMAN GROWTH HORMONE THERAPY (RHGH) FOR ALL LICENCED INDICATIONS

No.	Standard	Reference(s)
GENERAL RECOMMENDATIONS		
1 Specialist/Network centre accreditation		
	All centres should have a database of children/young people treated with rhGH including the indication for therapy	Consensus and (1)
2 Equity of service		
	a. All children and adolescents fulfilling the licensed indications will be offered treatment with rhGH	(2)
	b. Off-label treatment with somatotropin should only be initiated by a tertiary paediatric endocrinologist and the growth response reviewed after 4-6 months	(2)
3 Professional Expertise		
	Treatment with somatropin should always be initiated and monitored by a paediatrician with specialist expertise in managing growth disorders	(2-4)
4. Patient Experience		
	a The start of rhGH should be within 18 weeks of the time when specific eligibility criteria for rhGH therapy are met i.e. after a period of growth monitoring and investigation	(5)
	b. The expectation of the growth response should be discussed with the patient (if old enough) and parent(s) / carer(s) prior to commencing rhGH. The option and consequences of no treatment should also be outlined	Consensus
	c. The choice of rhGH delivery device should be decided following an informed discussion between the patient and parent(s) / carer(s) with the responsible clinician. This decision should be made on an individual basis taking into consideration the therapeutic need, license, and the likelihood of adherence to treatment	(2,6,7)
	d. Education of the parent(s) / carer(s) and patient (if old enough) by a designated appropriately trained health care professional should precede the start of rhGH. This should encompass information concerning the specific condition being treated, the rhGH preparation, administration and side effects	(2-4,8,9)
5. General recommendations		
	a. rhGH is self-administered or given by an adult, at home, as a daily subcutaneous injection	(2)
	b. Use of body surface area to calculate the rhGH dose is recommended in overweight/obese individuals to avoid inappropriately high GH doses	(10)
	c. Follow-up (a minimum of 6 monthly)* by a paediatrician (or delegated appropriately trained HCP) with specialist expertise in managing growth disorders in an OP clinic with accurate growth measurements	(1,2)

	* Unless more frequent reviews are recommended for a specific indication below. Consider 4-6 monthly review in the 1st year of rhGH therapy	
	d. Follow-up reviews should monitor bone age and document the response to rhGH treatment	(2-3,7)
	e. Consider plotting height on an appropriate, accurate condition-specific growth chart where available e.g. TS, NS	(11)
	f. If growth response is inadequate, the clinician should review the indication to treat, adherence to treatment and exclude additional pathology. In the absence of an adequate response to rhGH treatment after 12 months, consider stopping rhGH treatment	(2)
	g. Serum IGF-1 should be measured annually*. Conversion of IGF-1 levels to SDS can be helpful: Aim for IGF-1 levels ≤ +2.0 SDS above the mean for age. Consider reducing the rhGH dose if IGF-1 levels are > +3.0 SDS above the mean and use clinical judgement for IGF-1 levels between +2.0 to +3.0 SDS above the mean for age * Recommendations for target IGF-1 values during rhGH therapy are condition-specific and are included in the specific indication sections below.	Consensus and (12,13)
	h. Treatment with rhGH should be discontinued if any of the following occur: • Active malignancy • Poor response to therapy (growth velocity increases <50% from baseline in the 1st year) • Severe side effects e.g. intracranial hypertension • Insurmountable problems with adherence • Severe, acute critical illness (temporary discontinuation only)	(2,12,13,14)
	i. Routine GH dynamic testing is not required prior to commencing rhGH for conditions 1-6 unless there are specific clinical indications to assess GH production (see individual sections)	(1,2)
6. Management of rhGH at Transition for licensed indications 1-6		
	rhGH should be discontinued when: • Final height is reached • Epiphyses are fused • Height velocity < 2cm/year	(2)

SPECIFIC INDICATIONS FOR rhGH		
1. TURNER SYNDROME (TS)		
Eligibility		
	a. Confirmed genetic diagnosis of Turner Syndrome (TS) (karyotype) and/or phenotypic females with a karyotype containing one X chromosome and complete or partial absence of the second sex chromosome, associated with one or more typical clinical manifestations of TS TS karyotypes include: • 45,X • 45,X/46,XX • 45,X/47,XXX; 45,X/46,XX/47,XXX • 45,X/46,XY (phenotypic males) • 46,XX, del(p22.3); 46,X,r(X)/46,XX • 46,X i(Xq); 46,X,idic(Xp) • X-autosome translocation, unbalanced	(2,12)
	b. All children and adolescents with TS showing evidence of the following should be offered rhGH: • Height velocity <50th centile, observed over 6 months in the absence of other treatable cause(s) of poor growth • Child is already short e.g. familial short stature and short predicted height • Delayed presentation or TS diagnosis or already pubertal at the time of diagnosis • Initiation of rhGH treatment should be considered around 4-6 years old	(12)
Monitoring		
	a. Clinical evaluation 6 monthly for scoliosis during rhGH therapy and until growth is completed	(12)
	b. Annual review blood tests should also include thyroid function, HbA1c and coeliac screen	(12)
	c. Families should be counselled about the symptoms of intracranial hypertension and slipped capital femoral epiphysis during rhGH treatment, as individuals with TS are at higher risk of these complications compared with children being treated with rhGH for other indications	(12)
Management		
	a. rhGH dose 45-50 microgrammes/kg/day or 1.4mg/m^2/day* * Published data suggest that patients with a poor response to rhGH, and/or predicted unsatisfactory adult height with the standard rhGH dose alone and/or late presentation (short stature at pubertal onset) can be considered for oxandrolone 0.03-0.05 mg/kg/d (0.625-2.5mg daily) in conjunction with rhGH commencing at aged 8-10 years	(2,12,16,17)

2. PRADER-WILLI SYNDROME (PWS)		
Eligibility		
	a. Consider commencing rhGH therapy by 12 months of age	(18,19,20)
	b. A polysomnography sleep study should be undertaken and interpreted by the sleep medicine team prior to commencing rhGH	(18,19,20)
	c. In children presenting late with severe obesity and/or complications of obstructive sleep apnoea (OSA) or T2D, rhGH therapy should be considered on a case-by-case basis	(18,19,20)
	d. Poorly managed OSA and poorly managed T2D are contra-indications for rhGH treatment	(18,19,20)
Monitoring		
	A polysomnography sleep study is mandatory before commencing rhGH treatment and 2-3 months later. Central sleep apnoea requires assessment but should not delay rhGH treatment. Management of moderate/severe OSA is required before start of rhGH treatment	(20)
Management		
	a. Consider a smaller starting dose of rhGH 0.5 mg/m^2/day (9-15 microgrammes/kg/day) increasing to 1.0 mg/m^2/day (35 microgrammes/kg/day) over a period of 3-6 months (max. 2.7 mg/day)	(19)
	b. Total IGF-1 levels are frequently raised and do not always require GH dose reduction*. *Higher total IGF-1 concentrations could be accepted after assessment of other side effects of rhGH, especially if the IGFBP-3 is also elevated, as bioavailable IGF-1 may not be increased	(21,22,23)
	c. Scoliosis is not a contra-indication for rhGH treatment. RhGH treatment does not worsen scoliosis, but scoliosis can worsen during rapid periods of growth. Rapid progression should be managed in partnership with spinal surgeons	(24)
Transition		
	Research shows that PWS adults may gain benefit from rhGH treatment, but it is not licensed unless adult GHD is present* *Consider GH stimulation testing after at least 1 month off rhGH therapy. A GHRH-arginine test may be the most appropriate test as there are age- and BMI-related cut-offs. GH dosing in adults should follow NICE guidelines for treatment of adult GHD and requires titration of IGF-1 levels	(25,26)
3. CHRONIC RENAL INSUFFICIENCY (CRI)		
Eligibility		
	a. Consider rhGH for those with: • Chronic renal insufficiency • Dialysis >6 months of age **AND the following criteria**: Short stature (<2nd centile), short for mid parental height (>3 centile spaces below MPH centile) or slow growth (drop in	(14)

	height of > 1 centile space)	
	b. In children who have received a kidney transplant and have persistent growth failure, initiate rhGH therapy 1 year after transplantation if spontaneous catch-up growth does not occur and steroid-free immunosuppression is not a feasible option	(14)
	c. In children with CRI due to nephropathic cystinosis who have persistent growth failure, (defined as above), rhGH therapy should be considered at all stages of CKD	(14)
	d. Exclusion criteria: • Severe secondary hyperparathyroidism (PTH >500pg/ml) • Closed epiphyses • Known hypersensitivity to the active substance or to any of the excipients • Patients with proliferative or severe non-proliferative diabetic retinopathy • During the first year after renal transplantation	(14)
Assessments required prior to commencing rhGH for CRI		
	a. Before starting rhGH therapy, the following assessments are required: • Height (or supine length for patients below 2 years of age) should be regularly measured depending on age and chronic kidney disease (CKD) stage. Height velocity should be calculated over a minimum period of 6 months, and both height and height velocity should be compared with standardized growth charts. • Pubertal status assessment • Growth potential should be assessed by calculation of genetic target height based on parental height and the extent to which the epiphysis of the left wrist is open on radiography. Application of adult height prediction methods is not recommended for children with CKD • Age, primary renal disease, systemic disorders, stage of CKD, dialysis adequacy (for patients on dialysis) and graft function and glucocorticoid therapy (in children post-transplantation) should be considered when considering rhGH therapy • CKD-associated growth-limiting factors such as protein-calorie malnutrition, metabolic acidosis, electrolyte disturbances (hyponatraemia), dehydration and mineral dysregulation, including secondary hyperparathyroidism, should be adequately controlled before considering rhGH therapy	(14,15)
	b. The following investigations should be performed before starting rhGH: - Serum creatinine (and estimated GFR)	(14)

	- Urea - Calcium, phosphorus - Total alkaline phosphatase - Bicarbonate - PTH - 25(OH) vitamin D - Albumin - Fasting glucose and HbA1c - Serum TFT (TSH, fT3 and fT4) - IGF-1 - Fundoscopic examination - Bone age	
Management		
	a. rhGH dose 45-50 micrograms/kg/day OR 1.4 mg/m^2 /day	(2,14)
	b. Review every 3-6 months or more frequently for young patients and those with advanced CKD to monitor stature, height velocity, pubertal development, renal function, thyroid hormone levels (TSH and free T3 and T4), serum glucose, calcium, phosphate, bicarbonate and PTH	(14, 15)
	c. If height velocity in the first year of rhGH treatment is less than 2cm per year over baseline, we recommend assessment of patient adherence to rhGH therapy, including measurement of IGF-1, weight-adjusted rhGH dosage and assessment of nutritional and metabolic factors, as recommended before initiation of rhGH therapy	(14)
	d. rhGH should be discontinued: • At the time of renal transplantation • In patients with persistent severe secondary hyperparathyroidism (PTH >500 pg/ml)* • With occurrence of intracranial hypertension • In patients with slipped capital femoral epiphysis • If the patient does not adequately respond to rhGH treatment despite optimal nutritional and metabolic control • In patients with accelerated bone maturation • An unexplained decrease in estimated GFR *GH may be reinstituted when levels return to the desired PTH target range	(14)
4. BORN SMALL FOR GESTATIONAL AGE (SGA) WITH GROWTH FAILURE >4 YEARS OF AGE		
Eligibility		
	a. Eligibility for treatment: • SGA is defined as birth weight/length <-2.0 SDS* according to national or ethnicity specific growth charts (where available) • Growth failure is defined as a height <-2.5 SDS at 4 years*, parental adjusted height -1.0 SDS and height velocity < 0 SDS * NICE guidance includes a statement that SGA has been defined as birth weight < 10th centile. The licence for GH treatment of short stature SGA and international consensus state SGA is defined as birth weight/length <- 2.0 SDS † Silver-Russell syndrome consensus guidelines state that rhGH treatment should be made available from the age of two years to increase height and to optimise	(2,11,13,27, 28,29)

	body composition. rhGH should also be made available earlier in SRS if there is refractory hypoglycaemia.	
	b. Consider genetic evaluation if there are dysmorphic features, congenital malformations, microcephaly including screening for chromosomal breakage disorders e.g. Bloom syndrome which may be a contra-indication for rhGH therapy	(13)
	c. Treatable risk factors for growth failure such as nutrition, hypothyroidism, another chronic disease should have been addressed before considering rhGH therapy	Consensus
	d. Adding GnRHa treatment can be considered when short adult height is expected at pubertal onset	(13)
Monitoring		
	a. Assess for precocious puberty, bone age and thyroid, IGF-1, HbA1c	(13)
	b. Bone age is not useful for height prediction in SGA	(13)
Management		
	a. rhGH dose 35 micrograms/kg/day OR 1.0 mg/m^2 /day	(2)
	b. Consider rhGH discontinuation in cases of accelerated bone maturation	(13)
5. SHORT STATURE SECONDARY TO HOMEOBOX-CONTAINING GENE (SHOX) HAPLOINSUFFICIENCY		
Eligibility		
	a. Confirmed genetic diagnosis of SHOX gene haploinsufficiency and Turner Syndrome has been excluded Genetic diagnoses include: • A heterozygous partial or whole *SHOX* gene or *SHOX* enhancer region sequence deletion • Another heterozygous *SHOX* pathogenic sequence variant * NICE guidance does not specify specific height criteria to start rhGH, only that there has been evidence of growth failure	(2,30)
	b. Not all children and adolescents with pathogenic *SHOX* or *SHOX* gene enhancer region variants will have a short adult height. However, if a child or adolescent with a predicted pathogenic *SHOX* gene variant is short during childhood, the child or adolescent is likely to be at least as short as an adult or even shorter due a blunted pubertal growth spurt* *Birth length may be normal but followed by a low growth velocity until early childhood. The growth velocity may be normal until the onset of adolescence, when the growth velocity will likely be low	(2,30)
	c. In the absence of "growth" criteria for onset of GH therapy, the following are recommended: • Individual's height is <2.0 SDS below the population mean for chronological age and sex, and there has been a pre-treatment 6-month height velocity >1.0 SDS below the mean for bone age	Consensus
Monitoring		
	a. Bone age at the onset of treatment, and then at the	Consensus

	discretion of the clinician to assess rate of maturation of the bones (not more frequently than annually)* * Additional radiographic evaluations/referrals needed if the child or adolescent develops wrist pain, weakness, limitation of motion and/or deformity to rule out Madelung deformity	
Management		
	a. rhGH dose 45-50 microgrammes/kg/day OR 1.4 mg/m^2 /day	(2,17,30)
	b. Adjust rhGH dose to maintain IGF-1 levels within the upper half of the normal range for bone age (extrapolated if recent bone age unavailable). Tanner stage of puberty in combination with chronological age may be used if using an IGF-1 assay with reference ranges that are based on Tanner stages of puberty in combination with chronological age	Consensus
6. NOONAN SYNDROME (NS)		
Eligibility		
	a. A diagnosis of NS (clinical +/- genetic)	(31)
	b. In ~50% *PTPN11* defects are identified but other genes include *SOS1*, *RAF1* and *RIT1*. Genetic diagnosis may play a role in treatment decisions	(32)
	c. There is substantial overlap between normal growth and NS. This is about 50% up to age 8 years and at final height but less during puberty as there is also often pubertal delay	(33)
	d. The decision to treat is an individual one and depends on many factors including the underlying genetic diagnosis, adult height estimation, other developmental factors, and other NS comorbidities	Consensus
Monitoring		
	a. Pre-treatment monitoring should include auxology, echocardiography, clotting screen, FBC, renal USS, thyroid function tests, IGF-1 and bone age	(33)
	b. The auxological response to rhGH treatment should be repeated at least 6 monthly together with IGF1 until levels are stable	Consensus
	c. Repeat echocardiography should be repeated 6 monthly if there is any evidence of any hypertrophic cardiomyopathy. Liaison with cardiac follow-up should be undertaken	(33)
Management		
	a. rhGH dose of 33 microgrammes/kg/day b. Dose adjusted according to growth and IGF-1 levels* *The maximum dose should not exceed 66 microgrammes/kg/day OR 2 mg/m^2 /day	(31)
Transition		
	If GHD present, consider testing for adult GHD (see 2 Transition)	Consensus
PATIENT SUPPORT GROUPS		
	Turner Syndrome Support Society Prader Willi syndrome Association Child Growth Foundation – SRS, SGA, SHOX	

	Noonan Syndrome Association Restricted Growth Association UK	

References

1. https://www.bsped.org.uk/media/1580/uk-standards-for-paediatric-endocrinology-2019.pdf
2. https://www.nice.org.uk/guidance/ta188.
3. https://www.bsped.org.uk/media/1580/uk-standards-for-paediatric-endocrinology-2019.pdf.
4. https://www.england.nhs.uk/wp-content/uploads/2013/06/e03-paedi-medi-endo-diabet.pdf.
5. https://www.gov.uk/government/publications/right-to-start-consultant-led-treatment-within-18-weeks/referral-to-treatment-consultant-led-waiting-times-rules-suite-october-2022
6. Gau M, Takasawa K. Initial patient choice of a growth hormone device improves child and adolescent adherence to and therapeutic effects of growth hormone replacement therapy. J Pediatr Endocrinol Metab. 2017;30:989-993
7. BSPED Position Statement on Choice of Delivery Device for Growth Hormone Prescribing (2020): https://wwwbspedorguk/clinical-resources/position-statements/.
8. https://www.eurospe.org/media/2076/growth-hormone-deficiency-average-read.pdf.
9. https://www.eurospe.org/wp-content/uploads/2022/12/growth-hormone-deficiency-easy-read.pdf
10. Betts PR, Butler GE, Donaldson MDC, Dunger DB, Johnston DI, Kelnar CJH, Kirk J, Price DA, Wilton P. A decade of growth hormone treatment in girls with Turner syndrome in the UK. Archives of Disease in Childhood 1999; 80: 221-25.
11. https://www.bsped.org.uk/media/oo1hsxet/clinical-standards-for-growth-assessment-and-referral-criteria-for-children-with-a-suspected-growth-disorder.pdf
12. Clinical practice guidelines for the care of girls and women with TS: proceedings from the 2016 Cincinnati International TS meeting. Gravholt CH, Anderson NH, Conway GS et al. on behalf of the international turner syndrome consensus group. 2017 European Society of Endocrinology
13. Hokken-Koelega ACS, van der Steen M, Boguszewski MCS, Cianfarani S, Dahlgren J, Horikawa R, Mericq V, Rapaport R, Alherbish A, Braslavsky D, Charmandari E, Chernausek SD, Cutfield WS, Dauber A, Deeb A, Goedegebuure WJ, Hofman PL, Isganatis E, Jorge AA, Kanaka-Gantenbein C, Kashimada K, Khadilkar V, Luo XP, Mathai S, Nakano Y, Yau M. International Consensus Guideline on Small for Gestational Age (SGA): Etiology and Management from Infancy to Early Adulthood. Endocr Rev. 2023 Jan 13:bnad002. doi: 10.1210/endrev/bnad002. Epub ahead of print. PMID: 36635911.
14. Drube J, Wan M, Bonthuis M, Wühl E, Bacchetta J, Santos F, Grenda R, Edefonti A, Harambat J, Shroff R, Tönshoff B, Haffner D; European Society for Paediatric Nephrology Chronic Kidney Disease Mineral and Bone Disorders, Dialysis, and Transplantation Working Groups. Clinical practice recommendations for growth hormone treatment in children with chronic kidney disease. Nat Rev Nephrol. 2019 Sep;15(9):577-589.
15. https://www.bsped.org.uk/media/1588/renal-growth-guidelines-update-bsped-february-2019.pdf
16. Effect of oxandrolone therapy on adult height in Turner Syndrome patients treated with growth hormone: a meta-analysis Sheanon NM, Backeljauw PF 2015. International Journal of Paediatric Endocrinology
17. BNFC (British National Formulary for Children) | NICE (30/10/2022)
18. Passone CdGB, Franco RR, Ito SS, et al. Growth hormone treatment in Prader-Willi syndrome patients: systematic review and metaanalysis. BMJ Paediatrics Open 2020;4:e000630. doi:10
19. Grugni, G. & Marzullo, P. Diagnosis and treatment of GH deficiency in Prader-Willi syndrome. Best Pract Res Clin Endocrinol Metab 30, 785-794, doi:10.1016/j.beem.2016.11.003 (2016).
20. Deal C et al Growth Hormone Research Society Workshop Summary: Consensus Guidelines for Recombinant Human Growth Hormone Therapy in Prader-Willi Syndrome JCEM 2013, 98(6):E1072–E1087, doi: 10.1210/jc.2012-3888.
21. Tan, H. L. & Urquhart, D. S. Respiratory Complications in Children with Prader Willi Syndrome. Paediatr Respir Rev 22, 52-59, doi:10.1016/j.prrv.2016.08.002 (2017).
22. Feigerlová, E. et al. Elevated insulin-like growth factor-I values in children with Prader-Willi syndrome compared with growth hormone (GH) deficiency children over two years of GH treatment. J Clin

Endocrinol Metab 95, 4600-4608, doi:10.1210/jc.2009-1831 (2010).
23. Damen L, Elizabeth MSM, Donze SH, van den Berg SAA, de Graaff LCG, Hokken-Koelega ACS. Free Insulin-like Growth Factor (IGF)-I in Children with PWS. Journal of Clinical Medicine. 2022; 11(5):1280. https://doi.org/10.3390/jcm11051280
24. Bakker, N. E., van Doorn, J., Renes, J. S., Donker, G. H. & Hokken-Koelega, A. C. IGF-1 Levels, Complex Formation, and IGF Bioactivity in Growth Hormone-Treated Children With Prader-Willi Syndrome. J Clin Endocrinol Metab 100, 3041-3049, doi:10.1210/jc.2015-1410 (2015).
25. Grootjen, L. N. et al. Effects of 8 years of growth hormone treatment on scoliosis in children with Prader–Willi syndrome. Eur J Endocrinol 185, 47-55 (2021).
26. Frixou, M. et al. The use of growth hormone therapy in adults with Prader-Willi syndrome: A systematic review. Clin Endocrinol (Oxf) 94, 645-655 (2021).
27. Wakeling, E., Brioude, F., Lokulo-Sodipe, O. et al. Diagnosis and management of Silver–Russell syndrome: first international consensus statement. Nat Rev Endocrinol 13, 105–124 (2017). https://doi.org/10.1038/nrendo.2016.138
28. https://www.bsped.org.uk/media/hu3p0nw2/hgh-in-srs-position-statement-final.pdf
29. https://www.eurospe.org/wp-content/uploads/2022/12/igr-or-sga-average-readability.pdf
30. GeneReviews: Binder G and Rappold G: SHOX Deficiency Disorders, latest revision 2018. Adam MP, Ardinger HH, Pagon RA, et al., editors. Seattle (WA): University of Washington, Seattle; 1993-2022. https://www.ncbi.nlm.nih.gov/books/NBK1215/
31. Horikawa R, Ogata T, Matsubara Y, Yokoya S, Ogawa Y, Nishijima K, Endo T, Ozono K. Long-term efficacy and safety of two doses of Norditropin® (somatropin) in Noonan syndrome: a 4-year randomized, double-blind, multicenter trial in Japanese patients. Endocrine Journal 2020, 67 (8), 803-818
32. Zenker M, Edouard T, Blair JC, Cappa M. Noonan syndrome: improving recognition and diagnosis. Archives of Disease in Childhood 2022;107:1073-1078.
33. http://dyscerne.org/dysc/digitalAssets/0/265_Noonan_Guidelines.pdf