European Journal of Endocrinology, 2026, 194, R17–R36
https://doi.org/10.1093/ejendo/lvag013
Published: 16 January 2026
Invited review

International guideline on genetic testing of children with short stature

Andrew Dauber [1†], Alexander A.L. Jorge [2†], Ola Nilsson [3], Olaf M. Dekkers [4,5,6], Jesús Argente [7,8], Irene Netchine [9], Philippe Backeljauw [10], Jeffrey Baron [11], Debora R. Bertola [12], Peter Clayton [13], Justin H. Davies [14], Thomas Edouard [15], Thomas Eggermann [16], Evelien F. Gevers [17,18], Giedre Grigelioniene [19,20], Karen E. Heath [21,22], Youn Hee Jee [1,23], Pablo Lapunzina [22,24,25,26], Geert R. Mortier [27], Stepanka Pruhova [28], Helen L. Storr [29], Emma Wakeling [30], Carlos R. Ferreira [31], Tomonobu Hasegawa [32], Anita C.S. Hokken-Koelega [33], Agnes Linglart [34], Xiaoping Luo [35], Xiumin Wang [36], Vivian Hwa [37], Louise C. Gregory [38], Federica Buonocore [38], Mehul T. Dattani [38,39], Stefano Cianfarani [40,41,42]* and Jan M. Wit [43]

[1]Division of Endocrinology, Children's National Hospital, Department of Pediatrics, The George Washington University School of Medicine and Health Sciences, Washington, DC 20010, United States
[2]Genetic Endocrinology Unit (LIM25), Endocrinology Division, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP), São Paulo 01246-903, Brazil
[3]Division of Pediatric Endocrinology (ERN BOND, ENDO ERN) and Center for Molecular Medicine, Department of Women's and Children's Health, Karolinska Institutet and University Hospital, SE-17177 Stockholm, Sweden
[4]Department of Clinical Epidemiology, Leiden University Medical Center, 2333 ZA Leiden, The Netherlands
[5]Department of Endocrinology, Leiden University Medical Center, 2333 ZA Leiden, The Netherlands
[6]Department of Clinical Epidemiology, Aarhus University and Aarhus University Hospital, 8200 Aarhus, Denmark
[7]Departments of Pediatrics & Pediatric Endocrinology, Hospital Infantil Universitario Niño Jesús, La Princesa Research Institute, Department of Pediatrics, Universidad Autónoma de Madrid, 28006 Madrid, Spain
[8]Centro de Investigación Biomédica en Red Fisiología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III. IMDEA Food Institute, 28006 Madrid, Spain
[9]Sorbonne Université, INSERM, Centre de Recherche Saint Antoine, APHP, Hôpital Armand Trousseau, Explorations Fonctionnelles Endocriniennes, Paris 75012, France
[10]Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH 45229, United States
[11]National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892, United States
[12]Medical Genetics Unit, Pediatrics Department, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP), São Paulo 05403-000, Brazil
[13]Division of Developmental Biology & Medicine, Faculty of Biology, Medicine & Health, University of Manchester, M13 9PL, United Kingdom
[14]Regional Centre for Paediatric Endocrinology, Southampton Children's Hospital; Faculty of Medicine, University of Southampton, Southampton, SO16 6YD, United Kingdom
[15]Endocrine, Bone Diseases and Genetics Unit, Reference Centre for Rare Diseases of Calcium and Phosphate Metabolism (OSCAR Network, ERN BOND) and Reference Centre for Rare Diseases of Growth (FIRENDO Network, Endo-ERN), Children's Hospital, Toulouse University Hospital, 31300 Toulouse, France
[16]Center for Human Genetics and Genome Medicine, Medical Faculty, RWTH Aachen University, 52074 Aachen, Germany
[17]Centre for Endocrinology, William Harvey Research Institute, Faculty of Medicine, Barts and the London School for Medicine and Dentistry, Queen Mary University of London, London EC1M 6BQ, United Kingdom
[18]Department of Paediatric Endocrinology, Royal London Children's Hospital, Barts Health NHS Trust, London E1 1BB, United Kingdom
[19]Department of Clinical Genetics and Genomics, Karolinska University Hospital, SE-17176 Stockholm, Sweden
[20]Department of Molecular Medicine and Surgery, Karolinska Institutet, SE-17176 Stockholm, Sweden
[21]Institute of Medical & Molecular (INGEMM) and Skeletal Dysplasia Multidisciplinary Unit (UMDE-ERN BOND), Hospital Universitario La Paz, IdiPAZ, 28046 Madrid, Spain
[22]CIBERER-Centro de Investigación Biomédica en Red de Enfermedades Raras, ISCIII, 28029 Madrid, Spain
[23]Division of Endocrinology and Center for Precision Medicine and Genomics Research (PMGR), Children's Hospital, Department of Pediatrics, George Washington University School of Medicine and Health Sciences, Washington, DC 20010, United States
[24]Institute of Medical and Molecular Genetics (INGEMM), Hospital Universitario La Paz, IdiPAZ, 28046 Madrid, Spain
[25]ITHACA- European Reference Network for Rare Diseases, 28007 Madrid, Spain
[26]Department of Genetics, School of Medicine, UCJC University, 28692 Madrid, Spain
[27]Center for Human Genetics, University Hospitals Leuven and KU Leuven, B-3000 Leuven, Belgium
[28]Department of Pediatrics, Second Faculty of Medicine, Charles University in Prague and University Hospital Motol, V Uvalu 84, Prague 5 150 06, Czech Republic

Received: January 3, 2026. **Accepted:** January 7, 2026

[29]Centre for Endocrinology, William Harvey Research Institute, Barts and the London School of Medicine, Queen Mary University, London EC1M 6BQ, United Kingdom
[30]North East Thames Regional Genetics Service, Great Ormond Street Hospital for Children NHS Foundation Trust, London WC1N 3JH, United Kingdom
[31]Unit on Skeletal Genomics, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892-1103, United States
[32]Department of Pediatrics, Keio University School of Medicine, Tokyo 160-8582, Japan
[33]Department of Pediatrics, Erasmus University Medical Center, 3000 CA Rotterdam, The Netherlands
[34]Department of Endocrinology and Diabetes for Children, Paris Saclay University, AP-HP, INSERM, Bicêtre Paris Saclay Hospital, 94270 Le Kremlin Bicêtre, France
[35]Department of Pediatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China
[36]Department of Endocrinology, Genetics and Metabolism, Shanghai Children's Medical Center, Shanghai Jiaotong University School of Medicine, 1678 Dongfang Road, Shanghai 200127, China
[37]Premium Research Institute for Human Metaverse Medicine (WPI-PRIMe), The University of Osaka, Suita, Osaka 565-0871, Japan
[38]Genetics and Genomic Medicine Research and Teaching Department, UCL Great Ormond Street Institute of Child Health, 30 Guilford Street, London WC1N 1EH, United Kingdom
[39]Great Ormond Street Hospital for Children, London WC1N 3JH, United Kingdom
[40]Department of Systems Medicine, University of Rome 'Tor Vergata', 00133 Rome, Italy
[41]Endocrinology and Diabetes Unit, 'Bambino Gesù' Children's Hospital IRCCS, 00165 Rome, Italy
[42]Department of Women's and Children's Health, Karolinska Institutet, SE-17177 Stockholm, Sweden
[43]Department of Pediatrics, Willem-Alexander Children's Hospital, Leiden University Medical Center, 2333 ZA Leiden, The Netherlands

†Andrew Dauber and Alexander A.L. Jorge contributed equally.
*Corresponding author: Endocrinology and Diabetes Unit, "Bambino Gesù" Children's Hospital, IRCCS, Piazza S. Onofrio 4, Rome 00165, Italy. Email: stefano.cianfarani@uniroma2.it

Abstract

Short stature may be caused by a multitude of conditions, including genetic and non-genetic causes. Over the last decade, advances in genetic sequencing technologies have revolutionized our understanding of the underlying physiology of growth and greatly increased our ability to identify genetic etiologies of short stature. The current guideline provides a general overview of the approach to the evaluation of a child with short stature, followed by recommendations identifying factors in the medical and family history, physical examination, radiographic, and laboratory work up which increase the likelihood of identifying a genetic etiology. An algorithm is proposed for the genetic workup of individuals with short stature based on their clinical presentation. The benefits and risks of genetic testing are discussed as well.

Keywords short stature, growth, genetic causes, genetic syndromes, genome

Significance

This guideline is the first international consensus specifically addressing the use of molecular genetic testing in children with short stature of unknown cause. It represents an important step in redefining the evaluation of this common condition and is expected to have immediate impact on diagnostic practice, clinical decision-making, and counselling for many affected children and their families.

Introduction

Over the past two decades, the advancement and increased availability of genomic sequencing tools have provided numerous clinically significant insights into the etiology of short stature (SS), transforming the diagnostic approach to growth disorders and a wide range of congenital conditions. This guideline offers recommendations on the diagnostic evaluation of children with SS, focusing on indications for using currently available genetic tools. Recommendations are partly based on a systematic review and meta-analysis of the literature.[1] Definitions and abbreviations used in this paper are shown in Boxes 1 and 2.

The traditional definition of SS is based on a statistical cut-off, ie, a height of more than 2 standard deviations below the mean for sex and age based on appropriate population reference data, commonly expressed as a height standard deviation score (SDS) of <−2.0 (2.3rd percentile). In this guideline, the term SS is used for the presence of at least one out of three manifestations of growth failure: a height below −2.0 SDS; a decreasing height SDS over time (growth faltering); or a height SDS below the expected range around the sex-adjusted mid-parental height SDS (Box 3). The mid-parental height should not only be adjusted for parental sex (target height, TH[4]), but ideally also for assortative mating and parent–offspring correlations (conditional target height, cTH[2,5]).

Human height is a polygenic and heterogeneous trait, with its heritability reported to be approximately 80% based on estimates from twin studies.[6] Both rare and common genetic variants concurrently affect human height. According to genome-wide association studies (GWAS), a combination of >12 000 independent single-nucleotide variants (SNVs)

Box 1 Definitions

- In this guideline,
  - The word "child" is used for individuals between 0 and <18 years.
  - "Genetic testing" refers to any form of DNA sequencing, copy number analysis, karyotyping or methylation analysis.
  - A "genetic cause" includes any (likely) pathogenic chromosomal abnormality, structural variant (SV), copy number variant (CNV) or balanced alteration (eg, translocation), DNA sequence variant, or methylation defect for which sufficient evidence exists to show a causal relationship with the individual's symptoms.
  - "Short stature (SS)" is used for all manifestations of growth failure, ie, the presence of at least one out of three manifestations: a height below −2.0 SDS; a decreasing height SDS over time (growth faltering); or a height SDS below the lower limit of the statistically expected range around the sex-adjusted mid-parental height, expressed as the deviation from target height (TH) (height SDS-TH SDS < −1.5) or conditional target height (cTH, TH corrected for assortative mating and parent-offspring correlations) (height SDS-cTH SDS < −1.6)[2].
  - "Short SGA" individuals are defined as born small for gestational age (SGA) with persistent SS.
  - The term "isolated short stature" is used for short children born with a normal or low birth size in whom the diagnostic evaluation has not shown any additional clinical features.
  - "Chromosomal microarray (CMA)", as used here, encompasses all types of array-based genomic copy number analyses, including array-based comparative genomic hybridization (aCGH) and single nucleotide polymorphism (SNP) arrays[3]. CNVs can also be detected by software programs in genome sequencing data.
- The "standard deviation score (SDS)" of an individual's height is defined as the number of standard deviations above or below the mean for age and sex on a reference chart derived from the most recent respective population study.
- "Small for gestational age (SGA)" is defined as a reported birth weight and/or birth length below −2 SDS for gestational age.
- "Next-generation sequencing (NGS)" is a massively parallel sequencing technology that reads multiple DNA fragments in parallel with each other. Exome sequencing (ES) examines only exon sequences and intronic sequences nearby, ie, only protein coding DNA sequences, that include approximately 2% of human DNA. Genome sequencing (GS) reads all the bases in DNA, ie, includes exons, introns and non-coding intervening sequences. Both technologies can be used to examine single nucleotide variants (SNVs), small insertions and deletions, and copy number variations (CNVs) using different bioinformatic tools. GS can also detect other structural variants (SVs), such as balanced alterations (eg, translocations). However, some genomic rearrangements need to be confirmed using other methods [such as chromosome analysis, CMA, fluorescence in situ hybridization (FISH), optical genome mapping (OGM), or targeted sequencing of the breakpoints]. Both technologies can be used to sequence only a patient's DNA or in so-called family context when samples of biological parents or siblings can be used as reference samples for comparison. Currently, ES and GS use short reads. In a research setting, long read GS is available, a form of NGS that has technical advantages over short-read sequencing for the detection of specific types of genetic variations. It can sequence long strands of DNA or RNA without breaking them up into smaller fragments. Multiplex ligation-dependent probe amplification (MLPA) is a polymerase chain reaction (PCR) based method that uses probes to examine the copy number of a specific genomic region. Methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) is used, for example, in growth restricted imprinting disorders.

(generally with a population allele frequency >1%), clustered within >7000 non-overlapping genomic segments, covering about 21% of the genome, determines an individual's height potential.[7] While each of these common genomic variants has a very small effect on one's height (each contributing <2 mm), in aggregate, they can explain about half of the heritability and nearly half of overall phenotypic variation in height (reviewed in[8]). Additionally, rare variants with a larger impact on height variability (ranging from approximately 1–4 cm) also contribute to height determination in the general population.[8,9]

In individuals with SS, the condition may result from a single pathogenic variant following a clear monogenic inheritance pattern, which is both necessary and sufficient to explain the observed phenotype. In other cases, it may be attributed to a combination of two or more rare variants (digenic or oligogenic inheritance) or the interaction of common variants in a classical polygenic manner.[10-12]

It is commonly assumed that if a child's height SDS is close to (c)TH SDS, a polygenic etiology may be most likely, and this is considered a benign condition leading to an adult height that is close to (conditional) target height.[13] However, monogenic causes can also be found in such patients, especially autosomal dominant gene variants if one or both parents are short.[14] Another benign condition associated with SS in childhood and early adolescence is the slow maturation of the epiphyseal

Box 2 Abbreviations used ≥2 times

- AP, anterior-posterior
- BA, bone age
- CDGP, constitutional delay of growth and puberty
- CMA, Chromosomal microarray (see definition)
- CNV, copy number variant
- ES, exome sequencing
- GH, growth hormone
- GHD, growth hormone deficiency
- GS, genome sequencing
- IGF-1, insulin-like growth factor 1
- NGS, next-generation sequencing
- PCR, polymerase chain reaction
- QF-PCR, Quantitative Fluorescent Polymerase Chain Reaction
- rhGH, recombinant human growth hormone
- SDS, standard deviation score
- SGA, born small-for-gestational age
- SH/H, Sitting height/height ratio
- Short SGA, born small for gestational age (SGA) without catch-up growth
- SRS, Silver-Russell syndrome
- SS, Short stature (see definition)
- SV, structural variant

growth plates. When this is combined with the late onset of puberty, it is termed "constitutional delay of growth and puberty (CDGP)". This condition typically results in a normal adult height.[15]

Methods

International growth genetics guideline consortium

The work on this guideline was initiated by the Clinical Practice Committee of the European Society for Paediatric Endocrinology (ESPE). First, a small steering committee (A.D., A.A.L.J., M.D., J.M.W., and S.C.) was set up to design the format of the guideline and invite the methodologist (O.M.D.) and pediatric endocrinologists and medical geneticists with special expertise in genetic testing of short children to participate in the International Growth Genetics Guideline Consortium (IGGGC) (early 2024). The Presidents of the European Society of Human Genetics and the American College of Medical Genetics were informed. The consortium ($n = 34$) consists of 21 pediatric endocrinologists, 10 medical geneticists, 2 clinical laboratory geneticists, and 1 clinical epidemiologist/endocrinologist. ESPE was the only sponsor and funded all costs related to the initiative.

At the start of the guideline process, the guideline panel formulated two clinical questions regarding genetic testing of short children, resembling the questions that guide clinical decisions. The first is: "What is the diagnostic yield of genetic testing in children or adolescents with SS in a non-selected population of short children or in populations selected for an additional clinical feature?" The following clinical features were chosen: estimated pattern of inheritance (autosomal dominant or recessive), restricted intrauterine growth (small for gestational age, SGA), microcephaly or relative macrocephaly at birth or at presentation, neurodevelopmental disorders, severity of SS, dysmorphic

Box 3 Potential benefits and risks of genetic testing in children with SS

Potential benefits

- Definitive diagnosis can be gratifying to patients and their families
- Allows for more accurate genetic counseling and prediction of recurrence in other children
- Obviates the need for further extensive diagnostic tests to determine the etiology of the child's SS
- Enables earlier diagnosis by identifying a genetic condition before full phenotypic expression, particularly important in younger children (eg, in genetic GHD or hypopituitarism, where rhGH can be started at 3–6 months of age without performing a GH stimulation test)
- Eliminates the need for GH stimulation tests
- Guides therapeutic decisions, eg, deciding on prescribing growth stimulating medication
- Detects diagnoses for which rhGH is contraindicated or should be given with caution
- Highlights the need to screen for significant comorbidities associated with the underlying condition and refer to other specialties as needed
- Informs testing of additional family members allowing for earlier recognition of additional cases in the family
- Detects secondary genetic variants with potential to prevent adverse outcomes for the patient and their relatives

Potential risks

- A false positive genetic diagnosis leads to incorrect assumptions about the cause of disease, resulting in unnecessary anxiety, mismanagement, and inappropriate testing and treatment.
- Uncertainties arising from variants of uncertain significance reported.
- Secondary findings, even if accurate, can lead to anxiety in the affected family and, if erroneously classified, expose individuals to unnecessary surveillance or diagnostic testing.
- Secondary findings can affect certain types of insurance coverage. Laws vary by region.

features, or abnormal body proportions. A subcommittee of IGGGC (O.M.D., A.D., J.M.W, O.N., and J.H.D., chaired by A.A.L.J.), in collaboration with staff members of A.A.L.J. and A.D., performed a systematic review on this clinical question.

Based on this systematic review,[1] the diagnostic yield of genetic testing in cases of SS of undefined cause varies according to both the methodology employed and the patient's phenotypic characteristics. Specifically, single-gene testing shows a diagnostic yield of 4.4% (95% CI 3.3%–5.7%), gene panels 21.6% (95% CI 15.1%–28.9%), chromosomal microarray (CMA) 16.3% (95% CI 8.1%–26.4%), and exome sequencing (ES) 33.3% (95% CI 26.4%–40.6%). Regarding phenotype, the diagnostic yield ranges from 15.1% (95% CI 10.4%–20.6%) in children labeled as idiopathic SS, to 50.8% (95% CI 43.2%–58.4%) in syndromic cases, and up to 69.8% (95% CI 61.1%–77.9%) in patients with clinical features suggestive of skeletal dysplasia. In the paragraphs of the guideline where the diagnostic yield of genetic testing in children with isolated or non-isolated SS is discussed, the results of ES are provided according to Scalco et al.[1]

The second clinical question was: "Will genetic testing in SS improve the outcomes of individual patients?" For this question, another subcommittee of IGGGC (J.A., J.B., P.C., Y.H.J, O.N., chaired by J.H.D.) was set up, which performed a literature search on a slightly reformulated version of this question ("What are the clinical consequences of genetic findings in children with isolated SS?"), using ten prevalent genetic causes of children presenting with isolated SS. The literature search focused on clinically relevant endpoints, including quality of life, adult height, risk of malignancy, management, and treatment. This clinical question formed the basis for a detailed conventional clinical review, presented as Information S4 to the guideline.

Based on the planned format of the guideline, nine working groups were formed, chaired by O.M.D., O.N., J.A., A.A.L.J., J.M.W., I.N., M.T.D., A.D., and A.L., to formulate draft recommendations and rationales. The reports of the working groups were combined into several consecutive versions of the guidelines, which were discussed and revised electronically. During the process, all participants completed conflict of interest forms, summarized in Conflict of Interest.

A semi-final version served as a discussion document for an 8-hour hybrid meeting in May 2025 with all available members of the consortium, where all recommendations and rationales were discussed and revised. Consensus was reached upon discussion and in some cases by voting. Minority positions were considered in the rationale behind recommendations.

Target groups and aims

The guideline has been developed for pediatric endocrinologists, adult endocrinologists, medical geneticists, clinical laboratory geneticists, and general pediatricians who care for children with growth disorders. The overall purpose of this guideline is to provide clinicians with practical guidance on the diagnostic approach to children with SS. In clinical practice, both the recommendations and the clinical judgement of treating physicians should be considered. Recommendations are not meant to replace clinical acumen and may need adaptation to local circumstances. We acknowledge that in low-resource settings, financial and other restrictions may prevent clinicians from following all the recommendations.

	Flow	Content of recommendations	R1-24
A	Differential diagnosis	Initial descriptive classification, etiological classification	R1
B	Genetic investigation	Collaboration between pediatric endocrinology and genetics, segregation analysis, testing of relatives, reanalysis of genetic data, benefit/risk ratio of genetic testing	R2-7
C	Medical and family history	General medical history, 3-generation pedigree, short-SGA, malformations, neurodevelopmental disorders, positive family history	R8-12
D	Physical examination	Deep phenotyping, test for Turner syndrome, auxology, (non-)syndromic	R13-16
E	Radiology	Hand-wrist X-ray for bone age and anatomic variants, skeletal survey	R17-19
F	Laboratory analysis	Laboratory work-up, targeted gene panel for severe growth hormone deficiency or insensitivity	R20-22
G	General recommendations	Genetic testing advised in case of positive diagnostic clues, avoid genetic testing in suspected CDGP or polygenic inheritance	R23-24

Figure 1 Overview of the purpose and flow of the guideline.

Summary of methods used for guideline development

For this guideline, we used "Recommendations, Assessment, Development, and Evaluation" (GRADE) as a methodological basis to inform the recommendations.[16] Recommendations were not only informed by the quality of the evidence, but also by potential desirable and undesirable effects, values, and preferences.[16,17] National contexts were also considered.

The recommendations are worded as "recommend" (strong recommendation) and "suggest" (weak recommendation). The quality of evidence behind the recommendations is classified as very low (⊕◯◯◯), low (⊕⊕◯◯), moderate (⊕⊕⊕◯), and strong (⊕⊕⊕⊕). A strong recommendation implies that virtually all well-informed stakeholders—including clinicians, patients, and policymakers—are expected to favor the proposed course of action. In contrast, a weak recommendation indicates that although the majority may follow the suggested management, a notable proportion may reasonably opt for an alternative approach.[18] Statements derived primarily from clinical expertise and consensus within the working group, rather than from systematic evidence appraisal, are categorized as "good clinical practice" and are not assigned a formal grade. Recommendations that lack both a clear evidence base and consensus-derived clinical rationale are not graded. Formal evidence assessment and grading were applied only to

recommendations directly addressing the predefined clinical questions. The recommendations are divided into seven sections, as summarized in Figure 1.

Review process

In October 2025, a draft of the guideline was reviewed by four experts in the field ("designated reviewers", see "Acknowledgments' section), the International Clinical Guideline Committee (ICGC) of the International Consortium of Pediatric Endocrinology (ICPE), regional societies of pediatric endocrinology, and regional societies of human/medical genetics. All comments and suggestions were then discussed and implemented as thought appropriate by the IGGGC (see Table S6). After incorporation of comments from reviewers and various societies, formal endorsement was obtained from the European Society for Paediatric Endocrinology (ESPE), Pediatric Endocrine Society (PES), Latin American Society of Pediatric Endocrinology (SLEP), Chinese Society of Pediatric Endocrinology and Metabolism (CSPEM), Japanese Society for Pediatric Endocrinology (JSPE), European Society of Human Genetics (ESHG), Japan Society of Human Genetics (JSHG) and Human Genetics Society of Australasia (HGSA). All authors approved the submitted version of the manuscript.

Recommendations

Recommendation regarding the use of a diagnostic classification of SS (R1)

R1. We suggest using a descriptive classification after the initial assessment of the child with SS, followed by an etiological classification after complete evaluation.

Rationale

The clinician is expected to have a basic knowledge of the most prevalent and clinically relevant causes of SS and the diagnostic workup, including the available facilities for genetic testing. With a full initial clinical evaluation of the short child, consisting of a detailed medical and family history, physical examination, laboratory screening, and radiographic assessment, most secondary growth disorders,[19] such as celiac disease and hypothyroidism, can be diagnosed, as well as Turner syndrome in girls (Information S1, part 1).

When this initial clinical evaluation has not led to a diagnosis, we suggest categorizing short children into two main classes: (1) isolated SS (irrespective of birth size) and (2) non-isolated SS. Non-isolated SS can be further subcategorized into: 2a) suspected skeletal dysplasia; 2b) suspected defect in the growth hormone/Insulin-like growth factor-1 (GH/IGF-1) axis; and 2c) syndromic SS, including neurodevelopmental disorders (developmental delay, intellectual disability, autism spectrum disorder), microcephaly, congenital anomalies, facial and other dysmorphisms and major malformation (Information S1, part 1).

When the diagnostic workup is completed, the patient can be classified according to an etiological classification (Information S1, part 2). If no etiology has been found, the first subclassification is between isolated versus non-isolated SS, followed by

Table 1. Characteristics of current molecular genetic techniques

Molecular genetic exam	Ability to identify (epi-)genetic variants						Limitations	Cost[a]
	SNVs and InDels	CNVs (resolution)	Repeat expansions	Inversions or translocation	Uniparental disomy	berrant methylation		
Analysis approach based on candidate gene/region								
FISH	–	+/– (100 kb[b])	–	+/–[c]	–	–	Only regions with commercial probes	$$
MLPA	–	+/–– (< 1 kb[b])	–	–	–	–	Only regions with commercial kits	$$
MS-MLPA	–	+/– (< 1 kb[b])	–	–	Suggestive[c]	+	Only regions with commercial kits	$$
Single locus methylation test[d]	–	–	–	–	Suggestive[c]	+	No discrimination between aberrant methylation, UPD and CNV	$
Sanger sequencing	+	–	–	–	–	–		$
Panel NGS sequencing	+	+/– (< 1 kb[b])	–	–	–	–	Restricted number of genes	$$
DNA methylation epi-signatures	–	–	–	–	–	+	Only in leukocyte DNA; limited conditions; does not identify causal genetic variant	$$$$

(*continued*)

Table 1. Continued

Molecular genetic exam	Ability to identify (epi-)genetic variants						Limitations	Cost[a]
	SNVs and InDels	CNVs (resolution)	Repeat expansions	Inversions or translocation	Uniparental disomy	berrant methylation		
Hypothesis-free analysis (genomics approach)								
Karyotype	–	+/– (5-10 Mb)	–	+/–[e]	–	–	Requires cell culture and manual analysis by specialized cytogeneticist	$
CMA (SNP-array)	–	+ (50 kb[f])	–	–	+/–	–		$$
CMA (CGH-array)	–	+ (50 kb[f])	–	–	–	–		$$
Exome sequencing singleton	+	+/– (< 1 kb[g])	+/–[e]	+/–[e]	Suggestive[c]	–		$$
Exome sequencing trio/ family	+	+/– (< 1 kb[g])	+/–[e]	+/–[e]	+	–		$$$
Genome sequencing—short reads—singleton	+	+ (< 1 kb)	+/–[e]	+/–[e]	Suggestive[c]	–	Limitations in evaluating variants in intergenic, regulatory and deep intron regions	$$$
Genome sequencing—short reads—trio/ family	+	+ (< 1 kb)	+/–[e]	+/–[e]	+	–	Limitations in evaluating variants in intergenic, regulatory and deep intron regions	$$$$
Genome sequencing—long reads—singleton [d]	+	+ (< 1 kb)	+	+	Suggestive[c]	+	May require DNA extraction technique preserving large intact fragments	$$$$
Genome bisulfite sequencing (GBS) [d]	+	+ (< 1 kb)	+/–[e]	+/–[e]	Suggestive[c]	+	Requires additional complex bioinformatic pipelines for conversion	NA
Optical genome mapping (OGM)	–	+ (< 1 kb)	+/–[e]	+	Suggestive[c]	–	Requires DNA extraction technique preserving large intact fragments of DNA	$$$

Single locus methylation test includes high resolution melting analysis (HRMA); methylation-sensitive high resolution melting (MS-HRM) and pyrosequencing.
+ The test identifies the respective (epi-)genetic variants.
+/– The test identifies the respective (epi-)genetic variants to a limited extent.
– The test does not identify the respective (epi-)genetic variants.[a]Cost to the consumer. Comparison between the methods presented using $, $$, $$$, or $$$$. It is important to note that the availability and cost of genetic tests can vary significantly between countries, depending on local resources and healthcare systems. [b]Resolution of CNV detection limited to the analyzed regions. [c]Suggestive result needs to be confirmed by another method. [d]Tests available in research environment only. [e]Can identify, but with limitations. [f]Smaller CNVs might be detectable by targeted analysis. [g]Routine ES analysis is expected to include CNV assessment as a standard component. Greater sensitivity when it affects 3 or more exons.
Abbreviations: SNVs, single nucleotide variant; InDels, small insertions and deletions 1-50 pb; CNVs, copy number variants; FISH, fluorescence in situ hybridization; MLPA, multiplex ligation-dependent probe amplification; MS-MLPA, methylation-specific MLPA; CMA, chromosomal microarray analysis; CGH-array, comparative genomic hybridization array; SNP-array, single nucleotide polymorphism array; NGS, next generation sequencing; UPD, uniparental disomy.

further subclassification according to birth size. We suggest labeling the two subgroups of isolated SS of unknown origin (normal and low birth size) "Idiopathic isolated SS" [previously called "idiopathic SS (ISS)" according to the 2008 ISS consensus definition][2,5] and "idiopathic isolated short SGA", respectively.

Recommendations on genetic investigation in clinical practice (R2–R7)

In recent decades, numerous molecular techniques have been developed to analyse genetic and epigenetic variants. Many of these have been incorporated into the clinical evaluation of patients suspected of having a genetic condition, including children with SS. Clinicians must be familiar with the primary indications for each technique, as well as their limitations. They must also remain informed about regionally available genetic testing. Table 1 summarizes the types of genetic variants detected by currently available genetic diagnostic tools, including their limitations and comparative cost, and highlights their applications. The availability and cost of genetic tests vary significantly between countries.

R2. We recommend close collaboration between clinical laboratory geneticists, medical geneticists, and pediatric endocrinologists in the indication for genetic tests and interpretation of their results; genetic counseling is recommended for every family undergoing genetic testing. (Good clinical practice)

Rationale

Ideally, there is close collaboration between pediatric endocrinologists, clinical laboratory geneticists, and medical geneticists for the interpretation of genetic testing results in the context of clinical presentation. When requesting a genetic test, it is important to provide the patient's phenotypic data and family history in as much detail as possible to allow for a more accurate and effective analysis. When skeletal dysplasia is suspected, involvement of a pediatric radiologist is also crucial. A multidisciplinary clinic would be the ideal setting for communicating and discussing the results and implications of a genetic test with patients and their parents. The level of evidence of the association of a gene with a given phenotype is discussed in Information S2.

R3. We recommend that variant pathogenicity be classified by the clinically accredited laboratory according to published guidelines (ACMG/ACGS). (Good clinical practice)

Rationale

Guidelines for genetic variant interpretation incorporate multiple lines of evidence. The laboratory must classify genetic variants according to accepted guidelines, such as those of the American College of Medical Genetics and the Association for Molecular Pathology (ACMG/AMP) recommendations, and make sure to use the most recent version (see Information S2).[20] It is essential that the classification of any identified variant is explicitly contextualized in relation to the relevant phenotype and mode of inheritance. This information should be clearly presented in the report to allow for clinical interpretation and appropriate medical decision-making (see Information S2). However, for many variants identified in children with SS, it is difficult to definitively assign pathogenicity. Segregation analysis may be helpful (see **R4**) but is confounded by multiple factors, including assortative mating (the fact that short individuals tend to partner with other short individuals), incomplete penetrance, variable expressivity, and the existence of phenocopies. Thus, *in vitro* functional characterization can serve as a valuable adjunct tool to provide supporting evidence regarding the pathogenicity of a variant, when such data are available. This is not an easy task in the diagnostic setting, but it is important when treatment is available, or the child may be able to participate in a clinical trial, depending on the interpretation of the variant, or for preimplantation genetic testing for severe monogenic syndromic disorders.

Over the last few years, diagnostic laboratories have started to perform rapid functional assays where the results can influence variant interpretation in the clinical report,[21] although so far, this is rarely performed in clinical practice. These assays may include testing the effect of variants on splicing or the determination of a reduction or increase of RNA expression using quantitative real-time polymerase chain reaction (PCR) assays, and are only feasible when the gene is expressed in the most easily accessible tissues, such as blood or urine, or, if necessary, skin biopsies.

Additionally, for certain conditions, it is possible to identify a characteristic methylation profile (DNA methylation episignatures, Table 1) that defines the disease. This may provide supportive evidence for variant pathogenicity,[22] or gene expression signatures that can characterize a condition and indicate impact on functional pathways.[23]

R4. We recommend that segregation analysis should be performed in patients where it may alter the classification of the variant's pathogenicity. (Good clinical practice)

Rationale

Segregation analysis in parents and/or relatives can be helpful as a criterion for changing the classification of a Variant of Uncertain Significance (VUS) to likely pathogenic or benign. Therefore, in such patients, testing of other family members should be considered. However, especially in the context of a dominant inheritance model, variable expression and lack of penetrance must also be kept in mind when interpreting the segregation analysis.

R5. We recommend that testing of other family members should be considered when the identification of the same pathogenic variant in relatives could influence healthcare management and/or enable more precise genetic counseling (Good clinical practice).

Rationale

The decision to pursue familial analysis should consider the specific gene involved, the predicted inheritance pattern, and the associated phenotypes. Diagnostic variant screening in children should only be conducted if it provides a potential health benefit for the child.[24] This process should always be preceded by thorough genetic counseling, including a discussion of the potential benefits, limitations, and projected outcomes of testing.

R6. If the patient develops new clinical features, reanalysis of available genetic data should be performed. In children with persistently unexplained SS in whom genetic testing was previously performed, we recommend that reanalysis of genetic data be considered periodically, taking into consideration bioinformatic improvements and new genetic discoveries (Good clinical practice).

Rationale

Reanalyzing exome or genome data is recommended periodically due to the progression of genetic knowledge and technology.[25,26] Since the annotation of variants has improved after establishing vigorous quality control measures for ES around 2018,[27] resequencing should be considered for DNA samples tested before that time from patients with a high likelihood of a genetic cause but a previous negative test result. Additional resources for such re-evaluation of results over time should be provided by payers. This recommendation is based on the potential for new gene–disease associations, refinements in the classification of variants, and advancements in bioinformatics that can enhance diagnostic yield. [28,29]

R7. We recommend that the benefits and risks of the genetic investigation in a child with SS should be carefully discussed with the family on an individual basis in a pre-test appointment (Good clinical practice).

Rationale

Prior to embarking on genetic testing, one should carefully consider the potential benefits and risks of pursuing genetic investigations, summarized in Box 3. For a more detailed discussion on this topic, see Information S3 and the results of the literature review on the clinical consequences of ten prevalent genetic causes encountered in children with isolated SS (Information S4).

Recommendations regarding assessment of relevant diagnostic clues for a genetic cause of SS from the medical and family history (R8–R12)

In this and the three following sections (Figure 1), we present recommendations regarding diagnostic clues from the medical and family history (**section C, R8-12**), medical examination (**section D, R13-16**), radiographs (**section E, R17-19**) and laboratory investigations (**section F, R20-22**) that have been associated with an increased likelihood of a genetic cause and/or indicate a specific genetic cause of SS. These findings may guide the choice of test and the interpretation of results. We also summarize the evidence on whether the presence of these clinical features in fact increases the diagnostic yield of genetic testing.[1]

A proper medical assessment of a child with SS includes a detailed medical and family history, clinical examination, radiological assessment, and laboratory investigation. This should assist the clinician in preparing a differential diagnosis ranked according to the likelihood of a primary or secondary growth disorder [intrinsic or extrinsic to the growth plate, respectively, (Information S1)]. For general characteristics of these categories, see Information S5 and S6.

While for most secondary growth disorders, monogenic causes are rare, a monogenic cause can be relatively frequently found in primary growth disorders. Thus, after exclusion of a non-genetic secondary growth disorder, the clinician faces the challenge of estimating the likelihood of a genetic cause of the patient's SS. All genetic syndromes associated with SS (6037 entries in OMIM, May 2025) are associated with their own phenotypic profiles. These phenotypes have been expanding with the increasing use of next-generation sequencing (NGS), identifying more mildly affected individuals, leading to numerous syndromes with partially overlapping phenotypes.

R8. We recommend searching for diagnostic clues for a primary or secondary growth disorder from the medical history of the child and family, including a three-generation pedigree (Good clinical practice)

Rationale

A thorough medical history (including review of systems) and family history of the short child can offer important clues to the etiology. Secondary growth disorders (Information S6) can usually be suspected based on the clinical assessment and laboratory screening and confirmed through targeted laboratory testing. Identifying clinical information that increases the likelihood of a primary growth disorder of genetic origin (Information S5) can help guide genetic testing.

R9. In children born SGA with persistent isolated or non-isolated SS for whom no cause could be identified, we recommend thorough clinical evaluation for imprinting disorders, followed by specific DNA methylation testing where suspected. (⊕⊕◯◯)

Rationale

The underlying mechanism leading to being born SGA can involve maternal, placental, and/or fetal factors.[30] Therefore, SGA refers to a heterogeneous group of children with different etiologies and clinical outcomes. Most SGA-born children experience catch-up growth and achieve a height within their TH range, whereas approximately 5%-10% have persistent SS ("short SGA").[31]

Children with short SGA and clinical features suggestive of an imprinting disorder (such as Silver-Russell syndrome or Temple syndrome) should be investigated by DNA methylation testing. The decision to test should be guided by the Netchine-Harbison clinical scoring system (NH-CSS). Initial testing should include methylation analysis of imprinted loci on chromosomes 11p15, 7, and 14q32.[32,33] If negative, and if suspicion of a genetic syndrome remains, a family exome sequencing (ES) or genome sequencing (GS) trio is recommended to identify syndromic conditions with SS, including upd(14)mat.

R10. In children born SGA with persistent isolated or non-isolated SS for whom no cause could be identified and in whom recombinant human growth hormone (rhGH) treatment is considered, we recommend comprehensive genetic testing for diagnostic purposes (see algorithm) and to

identify rare genetic conditions in which rhGH treatment is contraindicated. (⊕⊕⊕◯)

As some etiologies of short SGA may increase cancer risk due to defects in DNA damage repair or replication[34], it is important to clinically evaluate all children with unexplained short SGA and perform genetic testing prior to rhGH initiation, especially when associated with microcephaly, dysmorphic features, developmental delay, and/or learning disability. A chromosomal breakage test with assessment of sister chromatid exchange can be used in such patients to screen for chromosomal instability disorders that have increased cancer risk, such as Bloom syndrome, Ataxia Telangiectasia, Fanconi anemia, and Nijmegen breakage syndrome.[35]

In a child with isolated SS, SGA status does not increase the likelihood of identifying a genetic etiology.[1] However, many children with syndromic growth disorders may also be born SGA, leading to higher rates of genetic diagnoses in the larger short SGA population.[36] An estimate of the diagnostic yield of genetic testing in short SGA through a conventional literature review is shown in Information S7. The current list of genetic causes associated with SS and increased cancer risk is presented in Information S8. In such patients, the risks and benefits should be carefully weighed and discussed thoroughly with the patient, allowing for shared decision-making as to whether to proceed with rhGH treatment.

R11. We recommend genetic testing in a short child with major malformations and/or neurodevelopmental disorders. (⊕⊕⊕◯)

Rationale

With a detailed medical history, symptoms of any organ or system dysfunction (eg, brain, heart, lung, kidneys, ears, eyes, skeleton, immune system, hemostasis) can be identified, and information can be collected on the presence of a neurodevelopmental disorder [developmental delay (DD), intellectual disability (ID) or neurological/behavioral symptoms, eg, autism spectrum disorder]. A neurodevelopmental disorder is an established indication for genetic testing irrespective of height.[37] A search of the OMIM database identified 1967 entries with SS and neurodevelopmental delay in the clinical synopsis (May 2025).

Based on the systematic review,[1] the diagnostic yield of genetic testing by ES is 15.1% (95% CI 10.4%-20.6%) in isolated SS, 50.8% (43.1%-58.4%) in syndromic SS, including those with neurodevelopmental disorders, and 69.8% (61.1%-77.9%) in skeletal dysplasias. For an estimate of the diagnostic yield of genetic testing in children presenting with various other potential diagnostic clues, see Information S9.

R12. We recommend genetic testing in a short child if the family history suggests autosomal dominant, autosomal recessive, X-linked, or mitochondrial inheritance, or if the child's height SDS is much shorter than that of both parents. (⊕⊕⊕◯)

Rationale

Evaluation of the inheritance pattern can help distinguish monogenic from polygenic causes. A three-generation pedigree, with information about parental consanguinity and heights of siblings, parents, grandparents, aunts and uncles, may help identify patterns of inheritance such as recessive, dominant, X-linked, or mitochondrial, or may raise the possibility of an imprinting disorder (for details, see Information S5 and S10). In a child with no family history of SS, genetic etiologies should still be considered. The cause of mild familial isolated SS is likely polygenic in most individuals.[38]

An autosomal dominant growth disorder is suspected if one parent has a similar height SDS as the short child. As noted earlier, due to assortative mating, autosomal dominant growth disorders may also be found if both parents are short. Recessive growth disorders are more commonly found in consanguineous families or in small and isolated communities but should also be suspected in non-consanguineous families when two or more affected siblings are born to unaffected parents. If maternal-side male relatives are short and the patient is a boy, X-linked inheritance of SS should be suspected. If no other family members are affected, an autosomal recessive, X-linked recessive, or *de novo* dominant inheritance should be considered.

Five studies have shown that having a family history of SS represented by at least one parent with height SDS < -2 significantly increases the diagnostic yield.[1]

Recommendations regarding assessment of relevant diagnostic clues for a genetic cause of SS from the physical examination (R13–16)

R13. We recommend performing a detailed clinical examination before referring for genetic testing. (Good clinical practice)

Rationale

A thorough physical examination (deep phenotyping) is essential in the clinical workup of a child with SS. Diagnostic clues for primary and secondary disorders are summarized in Information S5 and S6, respectively. The focus should be on the anthropometric assessment, which, in addition to height and weight measurements, should include head circumference, arm span, and sitting height. The pubertal stage should be evaluated. Assessing the presence of dysmorphic features, skin abnormalities, skeletal anomalies, and congenital malformations is also crucial for establishing clinical diagnoses, guiding genetic studies, and identifying potential candidate genes.

R14. We recommend assessing for Turner syndrome including its mosaic form by a validated genetic test in a girl with clinical features suggestive of Turner syndrome, as well as in any girl with unexplained SS. (⊕⊕⊕⊕)

Rationale

In textbooks and guidelines, it has been advised that karyotyping from peripheral blood should be performed in all girls with unexplained SS. This is based on observations that SS can be the only presenting sign of Turner syndrome and on the important clinical consequences of establishing the diagnosis.[39] If karyotyping is

used, a minimum of 30 metaphases should be analysed. Other validated methods besides karyotyping may be employed in certified laboratories, such as SNP-array or structural variant (SV) analysis in ES or GS based panels.

The diagnostic yield of this approach in girls with characteristic clinical features is assumed to be high. In contrast, the diagnostic yield of karyotyping in otherwise asymptomatic short girls has been reported as 2.5% in two small studies.[40,41] In a population-based epidemiological study, the age- and sex-specific cumulative incidence from birth until 16 years of age was 52 per 100 000.[42]

R15. We recommend genetic testing in a short child if the auxological assessment shows one of the following: severe SS (height < −3 SDS); microcephaly; macrocephaly (absolute or relative); or body disproportion (sitting height/height or arm span/height outside ±2.5 SDS). (⊕⊕⊕◯)

Rationale

Measurement of various auxological parameters (height, head circumference, and body proportions) is essential in the assessment of a short child. Although no studies have been reported where the impact of severe SS, microcephaly, or disproportionate SS has been investigated in isolation, circumstantial evidence from the literature suggests that the diagnostic yield of genetic testing of SS is increased with increasing severity of shortness or additional clinical features (Information S5).

Severe SS (height < −3 SDS)

While the presence of dysmorphic features or skeletal changes is probably the most important predictor of a genetic condition, the literature suggests that adults and children with severe isolated SS have an increased likelihood of establishing a genetic cause.[1] However, the presence of other clinical features in the reported patient cohorts,[43,44] does not allow for accurate quantification of the effect of the severity of SS.

Microcephaly and relative macrocephaly

The presence of microcephaly in a short child (irrespective of the severity of SS) may increase the diagnostic yield of genetic testing[45] and also points to specific etiologies, such as a heterozygous pathogenic *IGF1R* variant, cell cycle defect, or a DNA repair syndrome.[46] In two studies (heterogeneous in terms of patient characteristics), the presence of microcephaly in children with syndromic SS increased the diagnostic yield from 44% to 56%[45] and 25% to 83%[47].

Relative macrocephaly at birth is commonly seen in infants with Silver-Russell syndrome, Temple syndrome, 3M syndrome, and hypochondroplasia, among other genetic diseases. In most children with achondroplasia, relative macrocephaly progresses to true macrocephaly before the age of 2 years. No information is available on the impact of this feature on the diagnostic yield of genetic testing.[1]

Body disproportion

Several studies have reported that the presence of body disproportion (irrespective of the severity of SS) increases the diagnostic yield of genetic testing in short children, particularly in genes responsible for skeletal disorders. Unfortunately, most of these reports did not define or quantify body disproportion.[48-51] Body disproportion may become more evident as the child ages.

In short children with mild skeletal anomalies, significant differences were observed for sitting height/height (SH/H) SDS in patients with an identified pathogenic variant in bone dysplasia-associated genes (ie, *ACAN*, *IHH*) compared to those without.[52] In short children tested for *SHOX* haploinsufficiency, a SH/H ratio SDS >2[53-55] or [SH/H > 1 SDS or arm span ≥3 cm below height][56] may be useful predictive factors, although normal body proportions do not exclude *SHOX* haploinsufficiency. In three studies focused on single genes involved in growth plate cartilage regulation—*SHOX* (in two studies) and *NPR2* (in one)—an elevated SH/H SDS (>+2) was associated with a marked increase in diagnostic yield. Reported yields rose from 3.1% to 13.8%[54], 5.7% to 40%[57], and 17.6% to 28.3%[55], respectively.[1]

R16. We recommend genetic testing in a short child with clinical features suggestive of an underlying syndromic condition. (⊕⊕⊕⊕)

Rationale

Several studies have reported an increased diagnostic yield in short children who show features suggestive of a broader syndromic (genetic) disorder, either identified while taking the medical history (eg, neurodevelopmental disorders) or at physical examination (facial dysmorphism and/or one or more congenital malformations, eg, congenital heart disease).[1] For example, in a large cohort of 304 patients with SS who underwent ES, those with syndromic features (defined as a systemic abnormality), as compared to those with isolated SS, had a higher yield of genetic diagnoses (34% vs 11%).[58] In short SGA children, a prominent forehead and triangular face point to Silver–Russell syndrome.[59]

Recommendations regarding assessment of relevant diagnostic clues for a genetic cause of SS from the radiographic assessment (R17–19)

R17. We recommend performing a radiograph of the hand and wrist for bone age (BA) assessment in any child presenting with SS. Hand and wrist radiographs allow for the identification of anatomical variants, which may guide genetic investigation (Good clinical practice).

Rationale

A radiograph of the (left) hand and wrist provides information on the degree of BA delay or advancement. A delayed BA is typical for a secondary growth disorder [eg, juvenile hypothyroidism or growth hormone deficiency (GHD)] or for a general maturational delay, which may later present with delayed pubertal onset (then termed constitutional delay of growth and puberty, CDGP), considered a subclass of idiopathic isolated SS.[5] BA has limited utility below the age of 3 years.

Most primary growth disorders present with a normal or delayed BA, but in prepubertal children with heterozygous pathogenic variants in *ACAN*[60] or *GNAS*[61], an advanced BA is frequently observed.

The same radiograph can also provide information about anatomical abnormalities associated with genetic disorders. This can guide genetic investigations, particularly in children with isolated SS, who may carry defects in genes associated with growth plate function.[62] For example, the presence of a Madelung deformity is suggestive of *SHOX* haploinsufficiency. However, the radiological indications of skeletal dysplasia can be subtle, often making it difficult to recognize relatively mild forms of genetic skeletal disorders.[63] For examples, see Information S11.

R18. We recommend performing a skeletal survey (a series of radiographs that examine representative parts of the skeleton) in short children suspected of having a skeletal disorder, especially in the presence of disproportionate SS, bone deformities, or bone mineralization abnormalities.

Rationale

The evaluation of skeletal surveys in childhood in combination with other clinical findings (eg, clinical photographs and growth charts) should ideally be performed by an experienced pediatric radiologist or clinician trained to recognize the characteristic radiographic patterns associated with a specific skeletal dysplasia or group of skeletal disorders.[64-66] Diagnosis of a genetic skeletal disorder can often be suggested by particular radiographic findings, so-called radiographic pattern recognition, but the final diagnosis should be confirmed by genetic testing. Ideally, reports should include systematized terms such as those described in the Human Phenotype Ontology (HPO), allowing incorporation into ES/GS analyses for variant and gene prioritization.

To date, more than 770 distinct genetic skeletal disorders have been described, which may result in various anomalies in the shape and size of specific bones in the skeleton.[64] Good clinical indicators for a skeletal dysplasia include disproportionate SS, brachydactyly, pathological fractures, cranial nerve palsies (in the absence of a neuromuscular disorder), limb asymmetry, severe/progressive kyphoscoliosis, restricted or increased joint mobility, and waddling gait.

The following radiograms are recommended for a comprehensive survey: anterior–posterior (AP) and lateral view radiographs of the skull and spine, AP views of the pelvis and all four extremities (unilateral, if no asymmetry), and AP views of the hands and feet. A more tailored approach may be warranted in certain situations. The radiation dose of such a skeletal survey is relatively low.[67] To further minimize the effects of radiation in the newborn, a "babygram" (AP and lateral views) is advised.[68]

R19. We recommend genetic testing in a short child with clinical or radiographic skeletal abnormalities. (⊕⊕⊕⊕)

Rationale

The presence of clinical or radiological skeletal abnormalities (Information S11) increases the diagnostic yield of genetic testing in short children.[1,43,45,69-71] For details of skeletal findings associated with specific skeletal dysplasias, see Spranger et al.[72]

Recommendations regarding assessment of relevant diagnostic clues for a genetic cause of SS from laboratory investigations (R20–22)

R20. We recommend that each child with SS should undergo a laboratory evaluation, either as a screening procedure or guided by clinical features. (Good clinical practice)

Rationale

The purpose of laboratory evaluation in short children, either in the form of a standardized screening or guided by clinical features, is to detect indications of a primary or secondary growth disorder. Similar to any other screening procedure, the benefit of diagnosing a treatable condition at an early stage (effectiveness) must be weighed against the costs. Pediatric textbooks and guidelines have suggested that laboratory screening of short children should be performed by a general pediatrician, so that easily diagnosable and treatable conditions (eg, hypothyroidism, celiac disease) would be detected and treated as early as possible.[5,73] Others have suggested that laboratory tests should be guided by clinical features rather than routinely applied to all patients with SS.[74] A list of potentially useful laboratory screening tests is shown in Information S12.

R21. We recommend genetic testing using next-generation sequencing [exome/genome (ES/GS) testing or a targeted gene panel] in a short child with severe growth hormone deficiency (GHD) and/or anatomical abnormalities of the hypothalamus/pituitary area known to be associated with genetic causes. (Good clinical practice)

Rationale

GHD may be isolated (IGHD) or combined with other hormone deficiencies (combined pituitary hormone deficiency, CPHD). Both belong to a spectrum of disorders under the umbrella of congenital hypopituitarism (CH), a heterogeneous and complex disorder associated with highly variable clinical phenotypes ranging in severity. Over the last four decades, pathogenic variants have been identified in numerous genes encoding hormones and their receptors, or developmental proteins, including transcription factors implicated in hypothalamo-pituitary (HP) development.[75-77]

Affected patients manifest different CH phenotypes, CPHD and IGHD being the most frequent. Less common phenotypes include septo-optic dysplasia (SOD) and holoprosencephaly (HPE) (Information S13, Table S3). Whilst some of the variants show classical autosomal recessive, autosomal dominant, and X-linked recessive inheritance, many of the variants are monoallelic and associated with variable penetrance. Carriers of the variant, often in the same family as the index patients, may manifest a milder clinical phenotype than the proband or no abnormalities. We therefore recommend caution in the interpretation of genetic findings that are not recessively inherited, particularly novel variants identified in genes with variable penetrance (see Information S13).

Table S4 summarizes the genes currently associated with CH and their mode of inheritance. The clinical and neuroimaging phenotypes associated with CH are extremely heterogeneous, with unpredictable endocrine deficiencies often evolving, particularly in patients with SOD or pituitary stalk interruption syndrome (PSIS),[78,79] making monitoring challenging and treatment complicated. Due to the increasing number of CH-related genes and the variability in phenotypes, next-generation sequencing (ES/GS or a panel-based approach) is currently the most efficient approach in identifying causative pathogenic variants and investigating the possibility of oligogenicity.[80,81]

Establishing the genetic cause of CH can have important clinical benefits. For example, the identification of Type 2 GHD due to an autosomal dominant pathogenic *GH1* variant should make the clinician aware of the potential appearance of other pituitary hormone deficiencies (ACTH, TSH, and gonadotropins).[82] Additionally, the identification of pathogenic variants in *PROP1* in patients with a pituitary mass can avert surgery, as this mass is likely to involute at a later stage.[83] Further, a mild "partial isolated GHD" (MIM 615925), characterized by slow growth and low, borderline, or even normal serum GH responses to a GH stimulation test, can be caused by a monoallelic pathogenic *GHSR* variant. Such patients show adequate catch-up growth on rhGH treatment.[84]

R22. We recommend a targeted gene panel or first-line candidate gene approach in the short child with characteristic clinical and laboratory features of insensitivity to growth hormone or IGF-1. (⊕⊕◯◯)

Rationale

SS due to GH/IGF-1 axis defects is associated with varying degrees of GH insensitivity (GHI). Carriers of some of these gene defects (eg, in *IGF1R*) present with IGF-1 insensitivity. The clinical features range from extreme pre- and post-natal growth failure with other physical and laboratory abnormalities to milder clinical phenotypes (Information S14). Many other genetic SS syndromes can also present with features of GHI, for example, RASopathies.[85,86] Furthermore, a similar clinical presentation (mild growth failure in combination with a borderline low serum IGF-1 and a normal serum GH response to a GH stimulation test) can also be caused by conditions with normal GH sensitivity.[84,87,88]

Developing a detailed pedigree is mandatory (**R8**), as genetic cases may be autosomal recessive or dominantly inherited. When the physical examination, laboratory assessment, and radiological findings are consistent with a severe, "classical" or typical, GHI presentation (decreased serum IGF-1 and normal or high result of a GH stimulation test),[89,90] a targeted gene panel approach is recommended, including *GHR, IGF1, IGFALS, PAPPA2, QSOX2, STAT3, and STAT5B*. If analysis directed at candidate genes does not identify causal variants, depending on the availability of resources and the degree of clinical suspicion for a genetic condition, consider expanding to ES or GS. Patients with heterozygous defects of *IGF1R* or carrying a 15q26.3 deletion are usually born SGA and present with (relatively) small head circumference. Serum IGF-1 is usually above the mean for age and sex at baseline and/or elevated during rhGH treatment.[91]

A milder or atypical GHI phenotype makes clinical diagnosis more difficult. ES/GS allows for testing a broader range of genes, along with the potential for novel gene discovery. Less than half of atypical GHI patients are genetically confirmed via targeted gene panel testing,[92] indicating that a broader SS gene panel may be more cost-effective. Additional information is provided in Table S5.

General recommendations regarding positive and negative indications to perform genetic testing in children with SS (R23–24)

R23. We recommend that genetic testing for SS (beyond laboratory screening, including testing for Turner syndrome in girls) is **not** indicated in a child with isolated SS suspected of constitutional delay of growth and puberty (CDGP) or with a strong suspicion of a polygenic origin. (Good clinical practice).

Rationale

Children who present with mild to moderate SS (a height SDS −2 to −2.5 SDS), slow growth, delayed BA, but a growth trajectory within the TH range when corrected for BA can be considered "slow maturers". There is often a family history of pubertal delay. These patients often show delayed pubertal onset in adolescence (females >13 years, males >14 years) and are subsequently labelled as CDGP. Since slow growth and delayed or absent puberty in girls are also characteristic signs of Turner syndrome, this should be excluded before the diagnosis of CDGP in a girl can be accepted (see **R14**). By definition, CDGP is a diagnosis of exclusion. Once puberty has started, growth progresses normally and may also be prolonged. Several gene variants have shown to be associated with delayed pubertal timing,[93] but so far, such genetic findings do not have consequences for clinical management.

Currently, a polygenic origin of SS cannot yet be confirmed in the clinic, but we postulate that the likelihood of a monogenic cause is low in a child with mild and isolated SS with borderline short and non-syndromic parents, no indication of autosomal dominant inheritance, and a height SDS close to the target height SDS (<10%). We assume that a polygenic origin is more likely in such patients.

R24. We recommend considering genetic testing in any child with SS in whom information from personal and family medical history, physical examination, radiological or laboratory findings suggests an increased likelihood of a genetic cause (defined as a monogenic condition, chromosomal aberration, CNV or methylation disorder, not a polygenic origin). (⊕⊕⊕⊕)

Rationale

Each child presenting with SS deserves a full medical assessment, with special attention to all known diagnostic clues for a

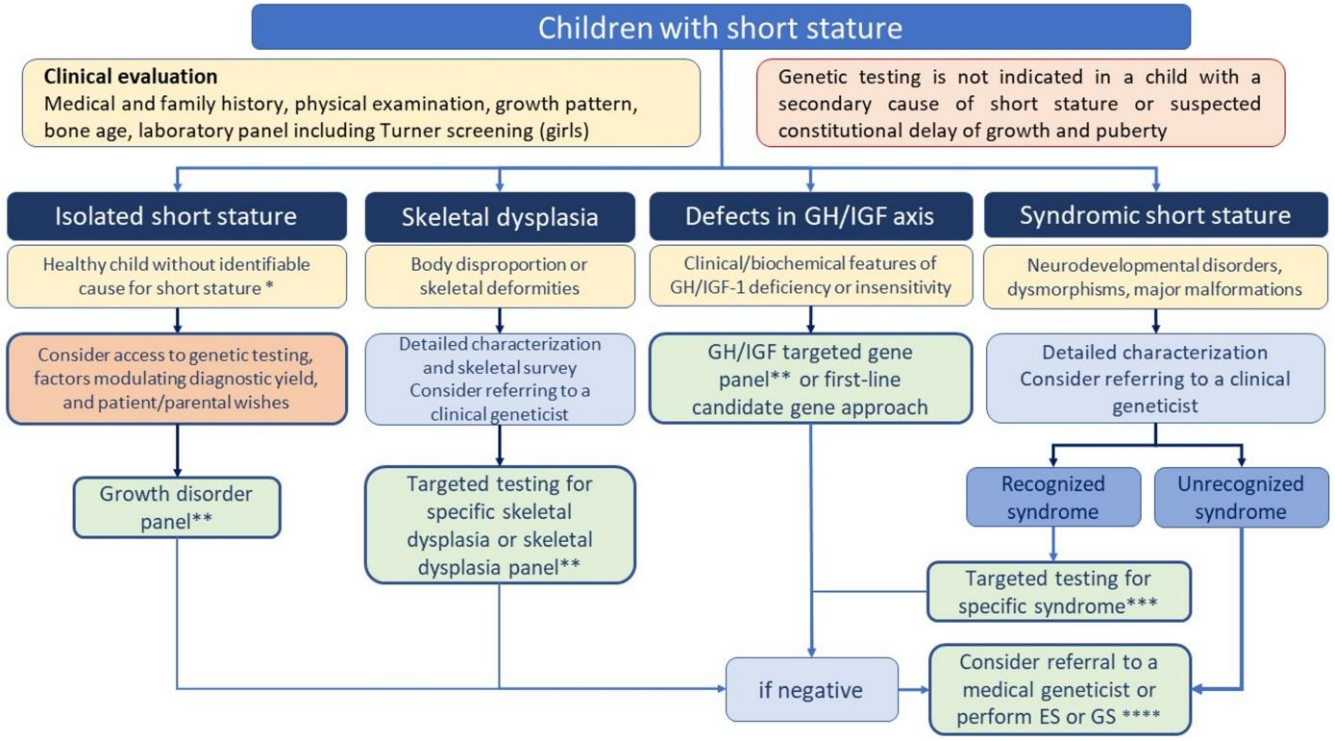

Figure 2 Algorithm for the diagnostic workup of children with short stature. After a full clinical evaluation and exclusion of non-genetic secondary growth disorders, further diagnostic investigations depend on the clinical presentation, with the following categories: isolated short stature, skeletal dysplasia, defects in the GH/IGF axis, and syndromic short stature. * Absence of neurodevelopmental disorder, body disproportion, dysmorphisms, or abnormal findings on radiographic or laboratory evaluation. ** In the (near) future, genome sequencing (short read or long read) will most likely become the standard approach in many countries, making targeted panels obsolete. Most panels are currently performed in silico, ie, genetic laboratories generate gene lists to analyse exome or genome sequencing data. *** In selected cases, the first line of molecular analysis should be methylation assessment of specific regions related to an imprinting disorder. **** Analysis of each case and the availability of resources should be considered in determining the best approach: exome sequencing (ES) or genome sequencing (GS); singleton, trio, or family analysis. In many cases, the use of ES incorporating CNV analysis can establish the diagnosis, but there is a growing application of genome sequencing (short and long read), which may become the preferred approach. The introduction of long-read genomic sequencing may also provide gene methylation information, allowing for the diagnosis of short stature disorders due to imprinting defects.

primary or secondary growth disorder. Current literature suggests that in children in whom a non-genetic growth disorder has been excluded and who present with one or more clinical or laboratory features known to increase the likelihood of a genetic cause, the diagnostic yield of genetic testing is sufficient to warrant genetic testing.[1]

Genes with the strongest evidence of association with isolated SS in the absence of other specific clinical findings are *ACAN*, *COL2A1*, *FBN1*, *FGFR3*, *GH1*, *GHR*, *GHSR*, *IGF1R*, *IHH*, *NF1*, *NPR2*, *PTPN11*, and *SHOX*.[1] This can thus be considered a minimum list of genes recommended for evaluation in children with isolated SS. Depending on the expertise of each center and advances in the field, additional genes may be considered. Variants in genes typically associated with syndromic SS or skeletal dysplasia should be interpreted with caution in patients lacking characteristic features.

Figure 2 shows the algorithm summarizing this recommendation. In most countries, ES with virtual panel analysis, or analysis of the entire exome, is the most commonly used strategy. Genome sequencing use is expected to expand in the future. We recognize that in resource-limited countries, genetic investigations may not be available or reimbursed.

Future perspectives

NGS, with the use of large gene panels, ES, and GS, has revolutionized the diagnostic approach to the short child with SS, as it has in many other areas of medicine. However, ES provides information only on protein-coding genes, which correspond to approximately 2% of the genome. Genetic testing can currently identify a monogenic cause in fewer than 15% of children with isolated SS, whereas up to 80% of children with syndromic SS or suspected skeletal dysplasia may receive a genetic diagnosis.[1] We assume that there are still further genes or novel genetic variants causing SS to be identified.

Current testing limitations will likely accelerate the adoption of GS to increase detection sensitivity for causative genetic variants. A recent study on genomes of a large cohort of families with suspected rare monogenic diseases has shown an incremental diagnostic yield of GS of approximately 8% for those who had previously undergone ES.[94] The main limitations to the large-scale use of GS are the higher analytical burden due to the millions of noncoding and structural variants that can be identified. Previously, high cost was also a limitation, but

currently, the cost of the combination of ES and CMA is similar to the cost of GS, so that several laboratories are currently using GS as a first-line test.[95] We expect that the progressive use of artificial intelligence and reduction of costs will lead to more widespread use of GS as a first-line single test. In the future, we anticipate that the integration of multi-omic approaches facilitated by long-read sequencing will allow for the identification of additional genetic etiologies of growth disorders. Compared with other sequencing technologies, long-read GS offers greater accuracy in characterizing structural variants, detecting repeat expansions, and providing epigenetic information (eg, methylation). It also facilitates the phasing of compound heterozygous variants without the need for parental analysis. For these reasons, long-read GS has the potential to become the leading sequencing approach in the future, driven by decreasing costs and advances in AI-assisted analytical methods. As these approaches are integrated into clinical practice, diagnostic rates will improve.[96]

With the growing discovery of regulatory and non-coding variants, understanding their transcriptomic impact will become increasingly important. We anticipate that RNA-sequencing will be incorporated into clinical practice to understand the potential impact of genetic variants on gene (mRNA) expression and that methylation signatures may play an increasing role in identifying genetic syndromes.

Digenic or oligogenic inheritance, where interaction of two or more genes located at different loci is observed, may account for a non-conventional pattern of inheritance underlying some forms of SS,[97] as shown in a subset of patients with Noonan syndrome.[98] A systematic search for the phenotype resulting from the interplay between two or more genetic variants (epistasis) has become feasible only with modern machine learning methods.[99] The importance of the multiple gene effect on the growth process has been further emphasized by the development of polygenic risk scores for predicting familial SS[100,101] and adult height,[102] showing an accuracy of 0.84–0.94. A polygenic risk score may help distinguish children with a benign, polygenic predisposition to SS[101] and also identify those who may have an underlying monogenic cause.[102]

In addition to sequence variants causing growth disorders, there is mounting evidence that epigenetic changes play a major role in the growth process. Epigenetic changes may directly affect transcriptional machinery or cause alterations in chromatin structure, making chromatin less or not accessible to transcription factors. The epigenetic processes that stably alter gene expression patterns (and/or transmit the alterations at cell division) include DNA (cytosine) methylation, post-translational modification of histone proteins, and remodeling of chromatin, and RNA-based mechanisms. Each of these epigenetic changes may have an impact on growth and is discussed in Information S15. Undoubtedly, with ongoing advances in genetic investigative technologies, the importance of genetic testing in the diagnostic workup of SS will continue to increase.

Acknowledgments

This research was supported in part by the Intramural Research Program of the National Institutes of Health (ZIA HD009024 to C.R.F.). The contributions of the NIH authors are considered Works of the United States Government. The findings and conclusions presented in this paper are those of the authors and do not necessarily reflect the views of the NIH or the U.S. Department of Health and Human Services. In October 2025, the near-final manuscript was circulated for comments to four designated reviewers: Dr. Margaret Boguszewski, Dr. Outi Makitie, Dr. Tom Ogata, and Dr. Ron Rosenfeld. We are grateful for their constructive comments which has led to improvement of the manuscript. The near-final manuscript was also made available to members of regional societies of pediatric endocrinology and of societies of human/medical genetics. The authors are grateful for the constructive comments by all reviewers, which led to further improvements (Table S6).

Authors' contributions

Andrew Dauber (Conceptualization [lead], Data curation [equal], Formal analysis [equal], Writing—original draft [lead], Writing—review & editing [equal]), Alexander A. L. Jorge (Conceptualization [lead], Data curation [equal], Formal analysis [equal], Writing—original draft [lead], Writing—review & editing [equal]), O. Nilsson (Conceptualization [equal], Writing—original draft [equal], Writing—review & editing [equal]), Olaf M. Dekkers (Conceptualization [equal], Data curation [equal], Formal analysis [lead], Writing—original draft [equal], Writing—review & editing [equal]), Jesús Argente (Conceptualization [equal], Writing—original draft [equal], Writing—review & editing [equal]), Irene Netchine (Data curation [equal], Writing—review & editing [equal]), Philippe Backeljauw (Formal analysis [equal], Writing—review & editing [equal]), Jeffrey Baron (Conceptualization [equal], Writing—review & editing [equal]), Debora R. Bertola (Data curation [equal], Writing—review & editing [equal]), Peter Clayton (Formal analysis [equal], Writing—review & editing [equal]), Justin H. Davies (Formal analysis [equal], Writing—review & editing [equal]), Thomas Edouard (Data curation [equal], Writing—review & editing [equal]), Thomas Eggermann (Formal analysis [equal], Writing—review & editing [equal]), Evelien F. Gevers (Formal analysis [equal], Writing—review & editing [equal]), Giedre Grigelioniene (Formal analysis [equal], Writing—review & editing [equal]), Karen E. Heath (Formal analysis [equal], Writing—review & editing [equal]), Youn Hee Jee (Formal analysis [equal], Writing—review & editing [equal]), Pablo Lapunzina (Formal analysis [equal], Writing—review & editing [equal]), Geert R. Mortier (Formal analysis [equal], Writing—original draft [equal]), Stepanka Pruhova (Data curation [equal], Writing—review & editing [equal]), Helen L. Storr (Formal analysis [equal], Writing—review & editing [equal]), Emma Wakeling (Data curation [equal], Writing—review & editing [equal]), Carlos R. Ferreira (Formal analysis [equal], Writing—review & editing [equal]), Tomonobu Hasegawa (Formal analysis [equal], Writing—review & editing [equal]), Anita C.S. Hokken-Koelega (Formal analysis [equal], Writing—review & editing [equal]), Agnes Linglart (Data curation [equal], Formal analysis [equal], Writing—review & editing [equal]), Xiao-ping Luo (Formal analysis [equal], Writing—review & editing [equal]), Xiumin Wang (Formal analysis [equal], Writing—review & editing [equal]), Vivian Hwa (Formal analysis [equal], Writing—review & editing [equal]), Louise C. Gregory (Formal analysis [equal], Writing—review & editing [equal]), Federica Buonocore (Data

curation [equal], Writing—review & editing [equal]), Mehul T. Dattani (Conceptualization [equal], Writing—original draft [equal], Writing—review & editing [equal]), stefano cianfarani (Conceptualization [equal], Formal analysis [equal], Project administration [lead], Writing—original draft [equal], Writing—review & editing [equal]), and Jan M. Wit (Conceptualization [lead], Data curation [equal], Formal analysis [lead], Writing—original draft [lead], Writing—review & editing [equal])

A.D, A.A.L.J., S.C., and J.M.W. contributed to the general design of the guidelines, the systematic review, chaired a working group and engaged in all aspects of the article. J.M.W. coordinated and edited the consecutive versions of the manuscript. O.N. contributed to the systematic review, chaired a working group and contributed to all aspects of the article. J.A. and I.N. chaired a working group and contributed to all aspects of the article. M.T.D. contributed to the general design and chaired a working group. O.M.D. served as methodology lead for the design of the guidelines and systematic review. P.B., J.B., D.R.B., P.C., J.H.D., T.Ed., T.Eg, E.F.G., G.G., K.E.H., Y.H.J., P.L, G.M., S.P., H.L.S., E.W., C.R.F., T.H., A.C.S.H-K, A.L., X.L., X.W., V.H., L.C.G. and F.B. contributed to the first versions of working group reports and contributed to all aspects of the article.

Supplementary material

Supplementary material is available at the *European Journal of Endocrinology* online.

Conflict of interest: A.D. reported receiving consulting fees and grants from Biomarin, BridgeBio, Novo Nordisk, and Pfizer. A.A.L.J. reported receiving consulting fees and grants from BioMarin, Novo Nordisk, and BridgeBio. O.N. reported serving as principal investigator in sponsored trials of Ascendis and Alexion, receiving consulting fees from Kyowa Kirin and speaker's honoraria from MSD. I.N. reported receiving a research grant from Merck and Pfizer and travel bursaries from Sandoz and Novo Nordisk. P.B. reported consulting fees from Novo Nordisk, Ascendis, BioMarin, Lumos, ICON, Tyra, and Eton. P.C. reported receiving consulting fees from Lumos and a research grant from Novo Nordisk. J.H.D. reported receiving consulting fees from BioMarin, KyowaKyrin, and SANDOZ, speaker's fees from MedEA, and a travel bursary from Novo Nordisk. T.Ed. reported receiving consultancy fees from Biomarin and Novo Nordisk. E.F.G reported receiving consultancy and speaker's fees and travel bursaries from Pfizer, Ascendis, Soleno, Radius Health, Novo Nordisk, Sandoz/Novartis, and Kyowa Kirin. She is PI for clinical trials of Novo Nordisk, Soleno, AstraZeneca, Merck, and Acadia. P.L. reported receiving consulting fees from Roche Institute and Pfizer. G.R.M. reported receiving consulting fees from Pfizer and Biogen, participating on a data safety monitoring board from Kyowa Kirin and Sanofi, and serving as principal investigator for Ipsen. S.P. reported receiving consulting fees from Novo Nordisk and Abbott. H.L.S. reported receiving a travel bursary from Novo Nordisk. T.H reported receiving research grants from Novo Nordisk and JCR Pharma. A.C.S.H-K reported receiving consultancy fees from Novo Nordisk and lecturing fees from Novo Nordisk and Merck. A.L. reported receiving consultancy fees from Novo Nordisk, speaker's fees from Merck Serono, Biogen, Kiowa Kirin, and Alexion, and served as principal investigator of a clinical trial for Pfizer. X.L. reported serving as principal investigator of clinical trials for GenSci and Novo Nordisk, and receiving consultancy fees from Nordisk, Amoytop, Visen, Ipsen, and Takeda. X.W. reported participating in research boards for Changchun and Genescience. M.T.D. reported receiving consultancy fees from Sandoz, Pfizer, Rhythm Pharmaceuticals, and Besins and lecturing fees from Novo Nordisk. S.C. reported receiving consultancy fees from Sanofi, Sandoz, and Novo-Nordisk. J.M.W. reported receiving consultancy fees from Aeterna Zentaris, Merck, and Lumos. O.M.D., J.A., J.B., D.R.B., T.Eg., G.G., K.E.H., Y.H.J., E.W., C.R.F., V.H., L.C.G and F.B. declared no competing interests.

Funding

The European Society for Paediatric Endocrinology (ESPE) provided financial support for the project. This covered the costs of the hybrid meeting at which all recommendations were discussed and agreed, as well as publication costs. No payments, honoraria, or travel expenses were made to the authors with respect to the preparation of this manuscript.

References

1. Scalco R, Schoones J, Galetaki D, et al. Diagnostic yield of genetic testing in children with short stature: a systematic review. *Eur J Endocrinol*. 2026. https://doi.org/10.1093/ejendo/lvag011
2. Hermanussen M, Cole J. The calculation of target height reconsidered. *Horm Res*. 2003;59(4):180-183. https://doi.org/10.1159/000069321
3. Miller DT, Adam MP, Aradhya S, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet*. 2010;86(5):749-764. https://doi.org/10.1016/j.ajhg.2010.04.006
4. Tanner JM, Goldstein H, Whitehouse RH. Standards for children's height at age 2 to 9 years allowing for height of parents. *Arch Dis Child*. 1970;45(244):819-819. https://doi.org/10.1136/ADC.45.244.819-B
5. Cohen P, Rogol AD, Deal CL, et al. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. *J Clin Endocrinol Metab*. 2008;93(11):4210-4217. https://doi.org/10.1210/JC.2008-0509
6. Jelenkovic A, Sund R, Hur YM, et al. Genetic and environmental influences on height from infancy to early adulthood: an individual-based pooled analysis of 45 twin cohorts. *Sci Rep*. 2016;6:28496. https://doi.org/10.1038/SREP28496
7. Yengo L, Vedantam S, Marouli E, et al. A saturated map of common genetic variants associated with human height. *Nature*. 2022;610(7933):704-712. https://doi.org/10.1038/S41586-022-05275-Y
8. Bicknell LS, Hirschhorn JN, Savarirayan R. The genetic basis of human height. *Nat Rev Genet*. 2025;26(9):604-619. https://doi.org/10.1038/S41576-025-00834-1

9. Grunauer M, Jorge AAL. Genetic short stature. *Growth Horm IGF Res.* 2018;38:29-33. https://doi.org/10.1016/j.ghir.2017.12.003
10. Gropman AL, Adams DR. Atypical patterns of inheritance. *Semin Pediatr Neurol*. 2007;14(1):34-45. https://doi.org/10.1016/j.spen.2006.11.007
11. Deltas C. Digenic inheritance and genetic modifiers. *Clin Genet*. 2018;93(3):429-438. https://doi.org/10.1111/CGE.13150
12. Kingdom R, Wright CF. Incomplete penetrance and variable expressivity: from clinical studies to population cohorts. *Front Genet*. 2022;13:1-25. https://doi.org/10.3389/FGENE.2022.920390
13. Rekers-Mombarg LTM, Wit JM, Massa GG, et al. Spontaneous growth in idiopathic short stature. European Study Group. *Arch Dis Child*. 1996;75(3):175-180. https://doi.org/10.1136/ADC.75.3.175
14. Plachy L, Strakova V, Elblova L, et al. High prevalence of growth plate gene variants in children with familial short stature treated with GH. *J Clin Endocrinol Metab*. 2019;104(10):4273-4281. https://doi.org/10.1210/jc.2018-02288
15. LaFranchi S, Hanna C, Mandel S. Constitutional delay of growth: expected versus final adult height. *Pediatrics*. 1991;87(1):82-87. https://doi.org/10.1542/peds.87.1.82
16. Langer G, Meerpohl JJ, Perleth M, Gartlehner G, Kaminski-Hartenthaler A, Schünemann H. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *Z Evid Fortbild Qual Gesundhwes*. 2012;106(5):357-368. https://doi.org/10.1016/j.zefq.2012.05.017
17. Dekkers OM, Burman P. ESE guidelines, why and how. *Eur J Endocrinol*. 2015;173(2):E1-E2. https://doi.org/10.1530/EJE-15-0625
18. Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation—determinants of a recommendation's direction and strength. *J Clin Epidemiol*. 2013;66(7):726-735. https://doi.org/10.1016/j.jclinepi.2013.02.003
19. Baron J, Sävendahl L, De Luca F, et al. Short and tall stature: a new paradigm emerges. *Nat Rev Endocrinol*. 2015;11(12):735-746. https://doi.org/10.1038/nrendo.2015.165
20. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015;17(5):405-424. https://doi.org/10.1038/gim.2015.30
21. Brnich SE, Rivera-Muñoz EA, Berg JS. Quantifying the potential of functional evidence to reclassify variants of uncertain significance in the categorical and Bayesian interpretation frameworks. *Hum Mutat*. 2018;39(11):1531-1541. https://doi.org/10.1002/HUMU.23609
22. Sadikovic B, Aref-Eshghi E, Levy MA, Rodenhiser D. DNA methylation signatures in Mendelian developmental disorders as a diagnostic bridge between genotype and phenotype. *Epigenomics*. 2019;11(5):563-575. https://doi.org/10.2217/EPI-2018-0192
23. Cuvertino S, Garner T, Martirosian E, et al. Higher order interaction analysis quantifies coordination in the epigenome revealing novel biological relationships in Kabuki syndrome. *Brief Bioinform*. 2024;26(1):1-14. https://doi.org/10.1093/BIB/BBAE667
24. Ross LF, Saal HM, Anderson RR, David KL. Ethical and policy issues in genetic testing and screening of children. *Pediatrics*. 2013;131(3):620-622. https://doi.org/10.1542/PEDS.2012-3680
25. Costain G, Jobling R, Walker S, et al. Periodic reanalysis of whole-genome sequencing data enhances the diagnostic advantage over standard clinical genetic testing. *Eur J Hum Genet*. 2018;26(5):740-744. https://doi.org/10.1038/S41431-018-0114-6
26. Manickam K, McClain MR, Demmer LA, et al. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021;23(11):2029-2037. https://doi.org/10.1038/s41436-021-01242-6
27. Corominas J, Smeekens SP, Nelen MR, et al. Clinical exome sequencing-mistakes and caveats. *Hum Mutat*. 2022;43(8):1041-1055. https://doi.org/10.1002/HUMU.24360
28. Wenger AM, Guturu H, Bernstein JA, Bejerano G. Systematic reanalysis of clinical exome data yields additional diagnoses: implications for providers. *Genet Med.* 2017;19(2):209-214. https://doi.org/10.1038/gim.2016.88
29. Schobers G, Schieving JH, Yntema HG, et al. Reanalysis of exome negative patients with rare disease: a pragmatic workflow for diagnostic applications. *Genome Med*. 2022;14(1):1-10. https://doi.org/10.1186/S13073-022-01069-Z
30. Lee PA, Chernausek SD, Hokken-Koelega ACS, Czernichow P. International Small for Gestational Age Advisory Board consensus development conference statement: management of short children born small for gestational age, April 24-October 1, 2001. *Pediatrics*. 2003;111(6):1253-1261. https://doi.org/10.1542/PEDS.111.6.1253
31. Hokken-Koelega ACS, van der Steen M, Boguszewski MCS, et al. International consensus guideline on small for gestational age: etiology and management from infancy to early adulthood. *Endocr Rev*. 2023;44(3):539-565. https://doi.org/10.1210/ENDREV/BNAD002
32. Wakeling EL, Brioude F, Lokulo-Sodipe O, et al. Diagnosis and management of Silver–Russell syndrome: first international consensus statement. *Nat Rev Endocrinol*. 2017;13(2):105-124. https://doi.org/10.1038/NRENDO.2016.138
33. Ogawa T, Narusawa H, Nagasaki K, et al. Temple syndrome: comprehensive clinical study in genetically confirmed 60 Japanese patients. *J Clin Endocrinol Metab*. 2025;110(9):e3041-e3051. https://doi.org/10.1210/CLINEM/DGAE883
34. Giacomozzi C. Genetic screening for growth hormone therapy in children small for gestational age: so much to consider, still much to discover. *Front Endocrinol (Lausanne)*. 2021;12:1-7. https://doi.org/10.3389/FENDO.2021.671361
35. Taylor AMR, Rothblum-Oviatt C, Ellis NA, et al. Chromosome instability syndromes. *Nat Rev Dis Primers*. 2019;5(1):64. https://doi.org/10.1038/s41572-019-0113-0
36. Homma TK, Freire BL, Honjo Kawahira RS, et al. Genetic disorders in prenatal onset syndromic short stature identified by exome sequencing. *J Pediatr*. 2019;215:192-198. https://doi.org/10.1016/J.JPEDS.2019.08.024

37. Srivastava S, Cole JJ, Cohen JS, et al. Survey of the landscape of society practice guidelines for genetic testing of neurodevelopmental disorders. *Ann Neurol*. 2024;96(5):900-913. https://doi.org/10.1002/ANA.27045
38. Silventoinen K, Sammalisto S, Perola M, et al. Heritability of adult body height: a comparative study of twin cohorts in eight countries. *Twin Res*. 2003;6(5):399-408. https://doi.org/10.1375/136905203770326402
39. Gravholt CH, Andersen NH, Christin-Maitre S, et al. Clinical practice guidelines for the care of girls and women with Turner syndrome. *Eur J Endocrinol*. 2024;190(6):G53-G151. https://doi.org/10.1093/EJENDO/LVAE050
40. Gicquel C, Gaston V, Cabrol S, Le Bouc Y. Assessment of Turner's syndrome by molecular analysis of the X chromosome in growth-retarded girls. *J Clin Endocrinol Metab*. 1998;83(5):1472-1476. https://doi.org/10.1210/JCEM.83.5.4805
41. Grandone A, Del Vecchio Blanco F, Torella A, et al. Multiplex ligation-dependent probe amplification accurately detects turner syndrome in girls with short stature. *Horm Res Paediatr*. 2016;86(5):330-336. https://doi.org/10.1159/000452219
42. Harju S, Saari A, Sund R, Sankilampi U. Epidemiology of disorders associated with short stature in childhood: a 20-year birth cohort study in Finland. *Clin Epidemiol*. 2022;14:1205-1214. https://doi.org/10.2147/CLEP.S372870
43. Huang Z, Sun Y, Fan Y, et al. Genetic evaluation of 114 Chinese short stature children in the next generation era: a single center study. *Cell Physiol Biochem*. 2018;49(1):295-305. https://doi.org/10.1159/000492879
44. Andrade NLM, Funari MF de A, Malaquias AC, et al. Diagnostic yield of a multigene sequencing approach in children classified as idiopathic short stature. *Endocr Connect*. 2022;11(12):1-10. https://doi.org/10.1530/EC-22-0214
45. Li X, Yao R, Chang G, et al. Clinical profiles and genetic spectra of 814 Chinese children with short stature. *J Clin Endocrinol Metab*. 2022;107(4):972-985. https://doi.org/10.1210/CLINEM/DGAB863
46. Juanes M, Guercio G, Marino R, et al. Three novel IGF1R mutations in microcephalic patients with prenatal and postnatal growth impairment. *Clin Endocrinol (Oxf)*. 2015;82(5):704-711. https://doi.org/10.1111/CEN.12555
47. Fang D, Li X, Zhang Z, et al. Clinical profiles and molecular genetic analyses of 98 Chinese children with short statures. *Front Genet*. 2024;15:1-11. https://doi.org/10.3389/FGENE.2024.1364441
48. Ezquieta B, Cueva E, Oliver A, Gracia R. SHOX intragenic microsatellite analysis in patients with short stature. *J Pediatr Endocrinol Metab*. 2002;15(2):139-148. https://doi.org/10.1515/JPEM.2002.15.2.139
49. Hirschfeldova K, Solc R, Baxova A, et al. SHOX gene defects and selected dysmorphic signs in patients of idiopathic short stature and Léri–Weill dyschondrosteosis. *Gene*. 2012;491(2):123-127. https://doi.org/10.1016/j.gene.2011.10.011
50. Plachy L, Dusatkova P, Maratova K, et al. Familial short stature-a novel phenotype of growth plate collagenopathies. *J Clin Endocrinol Metab*. 2021;106(6):1742-1749. https://doi.org/10.1210/CLINEM/DGAB084
51. Gippert S, Wagner M, Brunet T, et al. Exome sequencing (ES) of a pediatric cohort with chronic endocrine diseases: a single-center study (within the framework of the TRANSLATE-NAMSE project). *Endocrine*. 2024;85(1):444-453. https://doi.org/10.1007/S12020-023-03581-7
52. Sentchordi-Montané L, Benito-Sanz S, Aza-Carmona M, et al. High prevalence of variants in skeletal dysplasia associated genes in individuals with short stature and minor skeletal anomalies. *Eur J Endocrinol*. 2021;185(5):691-705. https://doi.org/10.1530/EJE-21-0557
53. Jorge AAL, Souza SC, Nishi MY, et al. SHOX mutations in idiopathic short stature and Leri–Weill dyschondrosteosis: frequency and phenotypic variability. *Clin Endocrinol (Oxf)*. 2007;66(1):130-135. https://doi.org/10.1111/J.1365-2265.2006.02698.X
54. Malaquias AC, Scalco RC, Fontenele EGP, et al. The sitting height/height ratio for age in healthy and short individuals and its potential role in selecting short children for SHOX analysis. *Horm Res Paediatr*. 2014;80(6):449-456. https://doi.org/10.1159/000355411
55. Vannelli S, Baffico M, Buganza R, et al. SHOX deficiency in children with growth impairment: evaluation of known and new auxological and radiological indicators. *Ital J Pediatr*. 2020;46(1):1-6. https://doi.org/10.1186/S13052-020-00927-Z
56. Joustra SD, Kamp GA, Stalman SE, et al. Novel clinical criteria allow detection of short stature homeobox-containing gene haploinsufficiency caused by either gene or enhancer region defects. *Horm Res Paediatr*. 2020;92(6):372-381. https://doi.org/10.1159/000507215
57. Plachy L, Dusatkova P, Maratova K, et al. NPR2 variants are frequent among children with familiar short stature and respond well to growth hormone therapy. *J Clin Endocrinol Metab*. 2020;105(3):e746-e752. https://doi.org/10.1210/CLINEM/DGAA037
58. Fan X, Zhao S, Yu C, et al. Exome sequencing reveals genetic architecture in patients with isolated or syndromic short stature. *J Genet Genomics*. 2021;48(5):396-402. https://doi.org/10.1016/J.JGG.2021.02.008
59. Eggermann T, Gonzalez D, Spengler S, Arslan-Kirchner M, Binder G, Schönherr N. Broad clinical spectrum in Silver–Russell syndrome and consequences for genetic testing in growth retardation. *Pediatrics*. 2009;123(5):e929-e931. https://doi.org/10.1542/PEDS.2008-3228
60. Gkourogianni A, Andrew M, Tyzinski L, et al. Clinical characterization of patients with autosomal dominant short stature due to Aggrecan mutations. *J Clin Endocrinol Metab*. 2017;102(2):460-469. https://doi.org/10.1210/jc.2016-3313
61. Mantovani G, Bastepe M, Monk D, et al. Diagnosis and management of pseudohypoparathyroidism and related disorders: first international consensus statement. *Nat Rev Endocrinol*. 2018;14(8):476-500. https://doi.org/10.1038/S41574-018-0042-0
62. Vasques GA, Andrade NLM, Jorge AAL. Genetic causes of isolated short stature. *Arch Endocrinol Metab*. 2019;63(1):70-78. https://doi.org/10.20945/2359-3997000000105
63. Chavhan GB, Miller E, Mann EH, Miller SF. Twenty classic hand radiographs that lead to diagnosis. *Pediatr Radiol*. 2010;40(5):747-761. https://doi.org/10.1007/S00247-009-1520-2

64. Unger S, Ferreira CR, Mortier GR, et al. Nosology of genetic skeletal disorders: 2023 revision. *Am J Med Genet A*. 2023;191(5):1164-1209. https://doi.org/10.1002/AJMG.A.63132
65. Handa A, Grigelioniene G, Nishimura G. Skeletal dysplasia families: a stepwise approach to diagnosis. *Radiographics*. 2023;43(5):1-20. https://doi.org/10.1148/RG.220067
66. Alanay Y, Lachman RS. A review of the principles of radiological assessment of skeletal dysplasias. *J Clin Res Pediatr Endocrinol*. 2011;3(4):163-178. https://doi.org/10.4274/JCRPE.463
67. Sait S, Havariyoun G, Newman H, Das S, Haque S. Effective radiation dose of skeletal surveys performed for suspected physical abuse. *Pediatr Radiol*. 2023;53(1):69-77. https://doi.org/10.1007/S00247-022-05477-6
68. Yu CC. Radiation safety in the neonatal intensive care unit: too little or too much concern? *Pediatr Neonatol*. 2010;51(6):311-319. https://doi.org/10.1016/S1875-9572(10)60061-7
69. Xiao H, Chen H, Chen X, et al. Comprehensive assessment of the genetic characteristics of small for gestational age newborns in NICU: from diagnosis of genetic disorders to prediction of prognosis. *Genome Med*. 2023;15(1):1-15. https://doi.org/10.1186/S13073-023-01268-2
70. Lin L, Li M, Luo J, et al. A high proportion of novel ACAN mutations and their prevalence in a large cohort of Chinese short stature children. *J Clin Endocrinol Metab*. 2021;106(7):E2711-E2719. https://doi.org/10.1210/CLINEM/DGAB088
71. Kim SJ, Joo E, Park J, Seol CA, Lee JE. Genetic evaluation using next-generation sequencing of children with short stature: a single tertiary-center experience. *Ann Pediatr Endocrinol Metab*. 2024;29(1):38-45. https://doi.org/10.6065/APEM.2346036.018
72. Spranger JW, Brill PW, Hall C, Nishimura G, Superti-Furga A, Unger S. *Bone Dysplasias*. Oxford University Press; 2018. https://doi.org/10.1093/med/9780190626655.001.0001
73. Wit JM, Kamp GA, Oostdijk W. Towards a rational and efficient diagnostic approach in children referred for growth failure to the general paediatrician. *Horm Res Paediatr*. 2019;91(4):223-240. https://doi.org/10.1159/000499915
74. Collett-Solberg PF, Ambler G, Backeljauw PF, et al. Diagnosis, genetics, and therapy of short stature in children: a growth hormone research society international perspective. *Horm Res Paediatr*. 2019;92:1-14. https://doi.org/10.1159/000502231
75. Kelberman D, Rizzoti K, Lovell-Badge R, Robinson ICAF, Dattani MT. Genetic regulation of pituitary gland development in human and mouse. *Endocr Rev*. 2009;30(7):790-829. https://doi.org/10.1210/ER.2009-0008
76. Fang Q, George AS, Brinkmeier ML, et al. Genetics of combined pituitary hormone deficiency: roadmap into the genome era. *Endocr Rev*. 2016;37(6):636-675. https://doi.org/10.1210/ER.2016-1101
77. Gregory LC, Dattani MT. The molecular basis of congenital hypopituitarism and related disorders. *J Clin Endocrinol Metab*. 2020;105(6):e2103-e2120. https://doi.org/10.1210/CLINEM/DGZ184
78. Cerbone M, Dattani MT. Progression from isolated growth hormone deficiency to combined pituitary hormone deficiency. *Growth Horm IGF Res*. 2017;37:19-25. https://doi.org/10.1016/j.ghir.2017.10.005
79. Cerbone M, Güemes M, Wade A, Improda N, Dattani M. Endocrine morbidity in midline brain defects: differences between septo-optic dysplasia and related disorders. *EClinicalMedicine*. 2020;19:100224. https://doi.org/10.1016/j.eclinm.2019.11.017
80. Simm F, Griesbeck A, Choukair D, et al. Identification of SLC20A1 and SLC15A4 among other genes as potential risk factors for combined pituitary hormone deficiency. *Genet Med*. 2018;20(7):728-736. https://doi.org/10.1038/gim.2017.165
81. Martinez-Mayer J, Vishnopolska S, Perticarari C, et al. Exome sequencing has a high diagnostic rate in sporadic congenital hypopituitarism and reveals novel candidate genes. *j Clin Endocrinol Metab*. 2024;109(12):3196-3210. https://doi.org/10.1210/CLINEM/DGAE320
82. Mullis PE, Robinson ICAF, Salemi S, et al. Isolated autosomal dominant growth hormone deficiency: an evolving pituitary deficit? A multicenter follow-up study. *J Clin Endocrinol Metab*. 2005;90(4):2089-2096. https://doi.org/10.1210/JC.2004-1280
83. Turton JPG, Mehta A, Raza J, et al. Mutations within the transcription factor PROP1 are rare in a cohort of patients with sporadic combined pituitary hormone deficiency (CPHD). *Clin Endocrinol (Oxf)*. 2005;63(1):10-18. https://doi.org/10.1111/J.1365-2265.2005.02291.X
84. Punt LD, Kooijman S, Mutsters NJM, et al. Loss-of-function GHSR variants are associated with short stature and low IGF-I. *J Clin Endocrinol Metab*. 2025;110(5):e1303-e1314. https://doi.org/10.1210/CLINEM/DGAF010
85. Malaquias AC, Jorge AAL. Activation of the MAPK pathway (RASopathies) and partial growth hormone insensitivity. *Mol Cell Endocrinol*. 2021;519:111040. https://doi.org/10.1016/J.MCE.2020.111040
86. Andrews A, Maharaj A, Cottrell E, et al. Genetic characterization of short stature patients with overlapping features of growth hormone insensitivity syndromes. *J Clin Endocrinol Metab*. 2021;106(11):E4716-E4733. https://doi.org/10.1210/CLINEM/DGAB437
87. Wit JM, Joustra SD, Losekoot M, Van Duyvenvoorde HA, De Bruin C. Differential diagnosis of the short IGF-I-deficient child with apparently normal growth hormone secretion. *Horm Res Paediatr*. 2021;94(3-4):81-104. https://doi.org/10.1159/000516407
88. Spiliotis BE, August GP, Hung W, Sonis W, Mendelson W, Bercu BB. Growth hormone neurosecretory dysfunction. A treatable cause of short stature. *JAMA*. 1984;251(17):2223-2230. https://doi.org/10.1001/jama.1984.03340410031028
89. Storr HL, Chatterjee S, Metherell LA, et al. Nonclassical GH insensitivity: characterization of mild abnormalities of GH action. *Endocr Rev*. 2019;40(2):476-505. https://doi.org/10.1210/ER.2018-00146
90. Savage MO, Storr HL, Backeljauw PF. The continuum between GH deficiency and GH insensitivity in children. *Rev Endocr Metab Disord*. 2021;22(1):91-99. https://doi.org/10.1007/S11154-020-09590-5
91. Walenkamp MJE, Robers JML, Wit JM, et al. Phenotypic features and response to GH treatment of patients with a

molecular defect of the IGF-1 receptor. *J Clin Endocrinol Metab*. 2019;104(8):3157-3171. https://doi.org/10.1210/JC.2018-02065
92. Cottrell E, Cabrera CP, Ishida M, et al. Rare CNVs provide novel insights into the molecular basis of GH and IGF-1 insensitivity. *Eur J Endocrinol*. 2020;183(6):581-595. https://doi.org/10.1530/EJE-20-0474
93. Howard SR. The genetic basis of delayed puberty. *Front Endocrinol (Lausanne)*. 2019;10:1-14. https://doi.org/10.3389/FENDO.2019.00423
94. Wojcik MH, Lemire G, Berger E, et al. Genome sequencing for diagnosing rare diseases. *N Engl J Med*. 2024;390(21):1985-1997. https://doi.org/10.1056/NEJMOA2314761
95. Runheim H, Pettersson M, Hammarsjö A, et al. The cost-effectiveness of whole genome sequencing in neurodevelopmental disorders. *Sci Rep*. 2023;13(1):1-8. https://doi.org/10.1038/S41598-023-33787-8
96. Vollger MR, Korlach J, Eldred KC, et al. Synchronized long-read genome, methylome, epigenome and transcriptome profiling resolve a Mendelian condition. *Nat Genet*. 2025;57(2):469-479. https://doi.org/10.1038/S41588-024-02067-0
97. Okazaki A, Ott J. Machine learning approaches to explore digenic inheritance. *Trends Genet.* 2022;38(10):1013-1018. https://doi.org/10.1016/j.tig.2022.04.009
98. Ferrari L, Mangano E, Bonati MT, et al. Digenic inheritance of subclinical variants in Noonan Syndrome patients: an alternative pathogenic model? *Eur J Hum Genet*. 2020;28(10):1432-1445. https://doi.org/10.1038/S41431-020-0658-0
99. Elgart M, Lyons G, Romero-Brufau S, et al. Non-linear machine learning models incorporating SNPs and PRS improve polygenic prediction in diverse human populations. *Commun Biol*. 2022;5(1):1-12. https://doi.org/10.1038/S42003-022-03812-Z
100. Lin YJ, Cheng CF, Wang CH, et al. Genetic architecture associated with familial short stature. *J Clin Endocrinol Metab*. 2020;105(6):1801-1813. https://doi.org/10.1210/CLINEM/DGAA131
101. Shelley JP, Shi M, Peterson JF, Van Driest SL, Simmons JH, Mosley JD. A polygenic score for height identifies an unmeasured genetic predisposition among pediatric patients with idiopathic short stature. *Genome Med*. 2025;17(1):1-13. https://doi.org/10.1186/S13073-025-01455-3
102. Lu T, Forgetta V, Richards JB, Greenwood CMT. Polygenic risk score as a possible tool for identifying familial monogenic causes of complex diseases. *Genet Med*. 2022;24(7):1545-1555. https://doi.org/10.1016/j.gim.2022.03.022