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**Review Article**

# EndoCompass project: research roadmap for growth disorders

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## Abstract

**Background:** Endocrine science remains underrepresented in European Union research programs despite the fundamental role of hormone health in human wellbeing. Analysis of the CORDIS database reveals a persistent gap between the societal impact of endocrine disorders and their research prioritization. At the national funding level, endocrine societies report limited or little attention of national research funding toward endocrinology. The EndoCompass project—a joint initiative between the European Society of Endocrinology and the European Society

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of Pediatric Endocrinology, aimed to identify and promote strategic research priorities in endocrine science to address critical hormone-related health challenges.

**Methods:** Research priorities were established through comprehensive analysis of the EU CORDIS database covering the Horizon 2020 framework period (2014-2020). Expert consultation in growth disorders was conducted to identify key research priorities, followed by broader stakeholder engagement, including society members and patient advocacy groups.

**Results:** Research priorities encompass genetic diagnosis of growth disorders; growth plate-targeted therapies; molecular mechanisms of Silver-Russell syndrome and imprinting disorders; hypothalamic dysfunction in Prader-Willi syndrome; and characterization of Noonan syndrome and tall stature conditions. Emphasis is placed on creating disease registries to facilitate outcome studies and developing precision therapeutics based on growth regulation pathways.

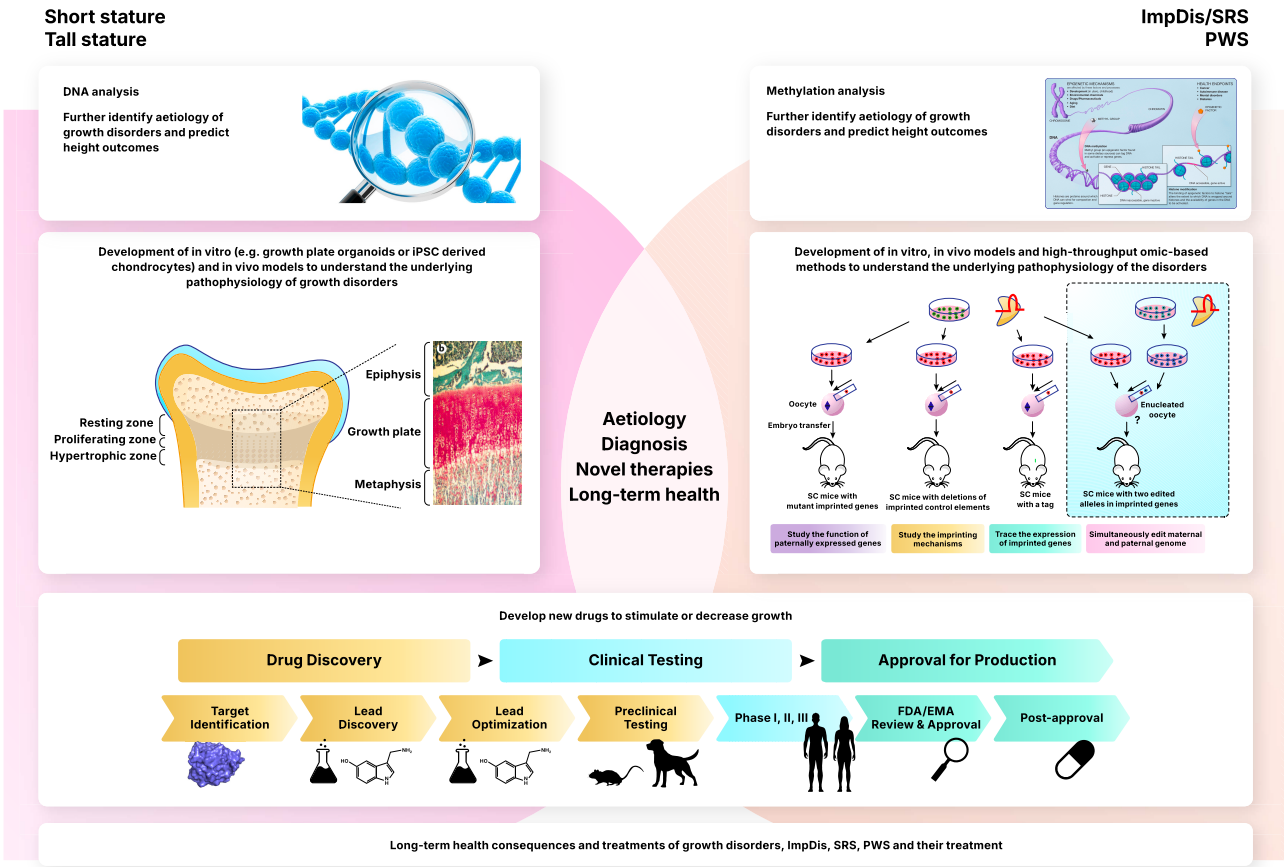
**Conclusions:** This component of the EndoCompass project provides an evidence-based roadmap for strategic research investment. This framework identifies crucial investigation areas into growth disorder pathophysiology, prevention, and treatment strategies, ultimately aimed at reducing the burden of these disorders on individuals and society. The findings support the broader EndoCompass objective of aligning research funding with areas of highest potential impact in endocrine health.

**Keywords:** short stature, growth hormone, Silver-Russell syndrome, imprinting disorders, Prader-Willi syndrome, Noonan syndrome, tall stature

## Significance

Endocrine research is underrepresented in EU research programmes, despite endocrine processes playing a vital role in human health. This chapter focuses on conditions of abnormal growth, specifically growth conditions due to growth hormone–insulin-like growth factor-1 axis and growth plate abnormalities, small for gestational age with failure to catch up, Silver–Russel syndrome and related methylation disorders, Prader–Willi syndrome, Noonan syndrome and other rasopathies, and overgrowth disorders. These conditions have associated metabolic, cardiovascular, and mental health risks, lower health-related quality of life, and thus have a large societal impact. The chapter sets out future research priorities for each of these conditions. Priorities include research into aetiology of growth conditions and prediction of outcomes, efficacy of growth-promoting drugs, development of models of disease (in vivo animal models, organoids, or induced pluripotent stem cells), new drug development, and consequences of the conditions in adulthood including development of databases and biobanks.

## Graphical Abstract



## Introduction

Growth during infancy, childhood, and adolescence is the result of a complex interplay of many factors. The control is mainly related to internal factors, such as genes and hormones, including growth hormone (GH) and insulin-like growth factors (IGFs), and to external factors, such as nutrition and environment.[1]

The hormones GH, secreted by the pituitary gland, and IGF-1, mainly produced by the liver, have leading roles in longitudinal growth, while other hormones, such as sex hormones, also contribute. GH and IGF-1 promote chondrocyte (cartilage cell) proliferation in the growth plates. The growth plate is a cartilage plate located at the end of long bones and vertebrae. Within the growth plate, chondrocytes are neatly organized into columns where they undergo rapid division, enlarge, and produce extracellular matrix. The extracellular matrix at the outer zone of the growth plate eventually calcifies and then transforms into bone. New chondrocytes are produced from chondroprogenitors and so continuously produce fresh growth plate cartilage, which eventually transforms into bone tissue. Consequently, the continuous formation of new cartilage, proliferation and enlargement of chondrocytes moves the growth plate further away from the center of the bone, and thus causes lengthening of bones, making children grow taller. Estrogen and testosterone, due to conversion to estrogen, promote growth plate ossification, eventually leading to the disappearance of the growth plate and thus cessation of growth.[2,3]

Some children have growth retardation, leading to short stature. Short stature is defined as a height less than or equal to a standard deviation score (SDS) of −2, equivalent to the 2.3rd centile, and thus has a prevalence of 1/43. Severe short stature (≤−3 SDS) has a prevalence of 1/1000 (0.1st centile). In 2019, UNICEF estimated that there were 144 000 000 children with short stature below the age of 5 years, worldwide.[4]

Studies suggest that GH deficiency, being small for gestational age (SGA) at birth, Silver-Russell syndrome (SRS), and other methylation disorders, Prader-Willi syndrome (PWS), Noonan syndrome, and skeletal dysplasias have associated metabolic, cardiovascular and mental health risks, and lower health-related quality of life, therefore having a large societal impact. For example, annual costs for PWS can be as high as €65 000 per patient.[5-14] However, much more research is warranted. More research is also required for the understanding of the underlying pathophysiology of many conditions associated with short stature.

Tall stature syndromes consist of a group of overgrowth −intellectual disability (OGID) syndromes and a group of conditions characterized by tall stature syndromes without an intellectual disability. The OGID syndromes are a heterogenous group of conditions characterized by increased height with or without increased head circumference, in association with an intellectual disability.[15] Tall stature syndromes without learning difficulties consist of a variety of conditions, of which Marfan syndrome is the most common.[16] However, most syndromes are rare, and the natural history and consequences for health and well-being are not well known. The molecular mechanisms of tall stature have not been fully elucidated, and many patients with tall stature syndromes have not had an underlying cause identified.

This chapter describes the epidemiology, associated pathology, social impact, and current knowledge in 5 fields of growth disorders, and then outlines the future research priorities for these fields.

## Short stature and GH, IGF-1, and growth plate disorders

### Epidemiology, societal impact, research state of art

As discussed above, short stature is defined as a height ≤−2 SDS, equivalent to the 2.3rd centile (with a prevalence of 1/43), whereas severe short stature (≤ −3 SDS) has a prevalence of 1/1000 (0.1st centile). Ten percent of those born SGA (height or weight ≤−2 SDS for gestational age) do not show catch-up growth,[17] and SGA with persistent short stature at age 4 occurs in 1/500.[6]

Around 80%-90% of the variation in adult height within a specific population is attributable to genetic factors. An individual's height is substantially determined by the additive effects of both common and rare genetic variants. Recent genome-wide association studies have identified over 7000 different loci associated with stature, covering approximately 21% of the genome.[18] In individuals with severe short stature, rare monogenic etiologies can now be found, and many of the genes involved relate to growth plate function.

For the past 4 decades, the primary treatment for short stature has been recombinant human GH, regardless of the underlying etiology. Additional efforts to increase height have included modulating the duration of the growth period, either through pubertal suppression using gonadotrophin-releasing hormone agonists, or by delaying epiphyseal closure using aromatase inhibitors. Rare patients with GH resistance are eligible for treatment with recombinant IGF-1.

As understanding increases regarding the diverse molecular etiologies of short stature, there is increased need for molecular stratification and novel precision therapeutics targeting these disorders. Currently, novel precision medicine approaches are being developed for specific skeletal dysplasias, such as C-type natriuretic peptide agonists for achondroplasia.[19] Further understanding of the genetic pathways involved in growth plate function and improved diagnostics of short stature are required, in order to improve care and develop more novel precision medicine approaches.

The long-term safety of GH treatment has been thoroughly studied in the last decade, but studies on long-term safety and efficacy of other treatments are lacking.[20]

### Future research priorities

The key future research areas in short stature, GH/IGF-1, and growth plate are in genetics, growth plate patho-physiology, and personalized medicine. They include strategies to (1) further identify the etiology of short stature and predict height outcomes, (2) assess current and develop new drugs to stimulate growth, (3) study response to growth-promoting therapies, and (4) assess effects of short stature/intrauterine growth retardation and treatment on health in adulthood.

#### Eetiology and prediction of height outcomes

- Improve methods, pathways, and gene panels to diagnose congenital growth failure/short stature of monogenic, polygenic, and epigenetic causes, and reduce diagnostic delay.

- Characterize interactions between multiple genetic variants, including abnormalities of GH and IGF-1 secretory and signaling pathways.
- Create large data sets for populations with short stature to assess genetic etiology and to create a genomic predictor of height/a polygenic risk score, including the effects of rare variants.
- Refine polygenic risk scores to accurately predict adult height in patients from all racial and ethnic backgrounds.
- Develop real-world evidence for the utility of genomic prediction models in clinical practice and develop digital tools that allow for integration of prediction models into clinical care.
- Develop a system to make an inventory of the phenotype of patients with genetic causes of short stature, so that the phenotypic spectrum of genetic causes is continuously updated.
- Develop personalized in vitro and in vivo models to understand the underlying pathophysiology of individual growth disorders. This could include development of easier access to individual patient's chondrocytes or other cell-based models, such as organoids, using patient-derived tissues.
- Increase insight in the cause and mechanism of absent catch-up growth after being born SGA.

**Current drugs and drug development**

- Develop new drugs for the treatment of short stature, including drugs directly targeting the growth plate.
- Assess the efficacy and safety of drugs developed for skeletal dysplasia, including achondroplasia, for the stimulation of growth in other forms of short stature.
- Explore the use of in vitro models to develop and test new drugs, for example growth plate organoids (growth plate in a dish) or induced pluripotent stem cell (iPSC)-derived chondrocytes, with introduction of specific mutations therein.
- Develop appropriately controlled clinical trials for definitive assessment of long-term safety and efficacy of aromatase inhibitors, and of delaying puberty, to increase adult height.
- Assess long-term safety and efficacy of long-acting GH drugs.

**Response to growth-promoting therapies**

- Explore the role of genetic variation, including genetic heterogeneity and rare genetic variants, in patients' responses to growth-promoting therapies and understand how to use these data to guide therapy for patients.
- Develop new and more accurate biomarkers of longitudinal growth, which can be used to assess treatment efficacy and accurately predict responses to growth-promoting therapy.
- Examine the use of personalized in vitro models to predict response to growth-promoting treatment.
- Develop and implement artificial intelligence (AI) and machine learning–based approaches to predict response to growth-promoting agents and direct choice of treatment.

**Long-term health throughout the lifespan**

- Characterize health problems in adult life in patients with syndromic and non-syndromic short stature, and intrauterine growth retardation, including quality of life assessments.
- Facilitate international collaboration to aggregate registry data for such current and long-term health outcomes and future growth-promoting therapies.
- Assess long-term effect and safety of pediatric IGF-1 treatment in adulthood.
- Assess quality of life and psychological well-being, for example social relationships, working capacity, and fatigue, in treated and untreated people with short stature during the lifespan, including research into prediction of who will gain most in terms of quality of life with growth-promoting treatment. This will help to find a balance between gain in quality of life, cost of treatment and healthcare budget.
- Study the degree, reasons and consequences of disparities, and perform research that aims to reduce disparities, in Europe and beyond

### Anticipated impact of the research

Improved diagnosis of growth disorders will have far-reaching benefits for the individual suffering from a growth disorder as well as for society as a whole. It would allow personalized medical monitoring and treatment of a larger proportion of patients, and also contribute to the development of novel, safe, and efficacious treatments.

Advances in our knowledge of the growth plate and our ability to model growth in vitro will also allow development and trials of drugs, which will ultimately improve outcomes, so improving quality of life. Advances in our ability to predict response to growth-promoting therapies, whether via genetic profiles, individualized disease models, or the use of AI, will allow practitioners to truly practice personalized precision medicine. Prediction of who will gain most in terms of quality of life from growth-promoting therapy will help to determine who should receive treatment in our changing society, with greater acceptance of inter-individual differences and scarce healthcare resources.

Gaining more knowledge about the prevalence and type of health problems in adults with short stature will lead to health risk awareness in professionals and patients, which will help to prevent long-term negative health outcomes.

## Silver-Russell syndrome and other imprinting disorders associated with short stature

### Epidemiology, societal impact, research state of art

Imprinting disorders such as SRS [Online Mendelian Inheritance in Man® reference (OMIM) #180860] and Temple syndrome (OMIM #616222) are increasingly recognized as important causes of short stature. However, they are frequently overlooked and misdiagnosed, as the clinical and molecular diagnosis is challenging. Making a diagnosis is key for bespoke management, treatment, peer support, and tailored health surveillance.

These conditions are multisystem disorders requiring multidisciplinary care and demanding significant health resources, particularly in childhood. The prevalence of imprinting disorders is more frequent than previously appreciated.[21] Evidence is accumulating that these conditions are associated with adverse cardiometabolic health.

Silver-Russell syndrome is associated with severe prenatal and postnatal growth retardation, characteristic features (relative macrocephaly, prominent forehead, and body asymmetry) and severe feeding difficulties.[22] The diagnosis is suspected upon the presence of 4 or more of these 6 items. The reported incidence of SRS ranges from 1/30 000 to 1/100 000 live births per year, but it is probably more common.

An underlying molecular cause is currently identified in around 60% of patients fulfilling the criteria of SRS. These include 30%-60% with loss of methylation (LOM; a molecular alteration) in 11p15 and 5%-10% with maternal uniparental disomy of chromosome 7 (UPD(7)mat). Rare mutations affecting *CDKN1C*, *HMGA2*, *PLAG1* and *IGF2* are also reported, together with imprinting defects responsible for Temple syndrome.[23]

However, 40% of individuals with a clinical diagnosis of SRS do not have a molecular diagnosis and are labeled "clinical SRS." A greater understanding of the genetic causes of clinical SRS is needed to optimize healthcare.

Children with SRS have phenotypic features in common with other imprinting disorders (eg, lack of appetite during infancy, growth failure, pubertal abnormalities, and high serum IGF-1 levels), while other features are distinct. The underlying causes explaining these similarities and differences are important for clinical care, but are as yet unknown. One hypothesis is that imprinted genes are co-regulated or that some genes have an impact on the expression of others, within a network of imprinted genes.[24,25] However, the mechanisms of regulation and interactions of most of the imprinted loci are far from being understood. Clinical features of SRS and effects of GH therapy during childhood have been reported,[22] but the consequences and optimal management of SRS and many of the rarer imprinting disorders across the lifespan are unknown.

## Future research priorities

Key future research in SRS and imprinting disorders focuses on the identification of the full spectrum of molecular alterations, their causes and functional consequences. By combining this knowledge with deep phenotyping, the clinical relevance of imprinting disturbances will be evaluated, and personalized clinical regimens can be developed. Another key research area regards the clinical consequences of SRS/ imprinting disorders across the lifespan. Specific aims to achieve these goals include the following.

### Building the base for research

- Create a pan-EU database of imprinting disorders that includes phenotypical and molecular data.
- Establish a biobank with samples from individuals with different imprinting disturbances.
- Generate suitable in vitro and in vivo models for imprinting disorders.
- Undertake comprehensive studies to determine the prevalence of imprinting disorders.

### Making use of new technology

Implement and use high-throughput omics technologies (genomics, epigenomics, transcriptomics, proteomics, and liquid biopsy) and AI, as follows:

- Identify genome-wide episignatures, in different tissues.
- Identify new imprinting disorders.
- Study (epi)genotype-phenotype correlations to explain the clinical features and predict prognosis.
- Improve the genetic testing algorithms and include prognostic markers.
- Develop single-cell transcriptome analysis for imprinting disorders.
- Characterize effects of imprinting defects in germ cells.
- Develop AI and machine learning to improve epidemiological insight, diagnosis, and prediction of future complications of imprinting disorders, eg, epigenetic methylation signatures, facial recognition, such as further improvement of the Face2Gene app).

### Identifying the causes of aberrant imprinting

- Decipher the molecular causes of imprinting defects (eg, enable genetic and reproductive counseling).
- Understand the regulation within imprinted regions, and the role of epigenetic regulation in human development.

### Understanding the impact of disturbed genomic imprinting

Delineate the functional impact of disturbed genomic imprinting on cellular processes and the clinical outcome, as follows:

- Study the functional interactions between imprinted genes and their products.
- Develop novel treatments for imprinting disorders using experimental in vitro/ex vivo/in vivo models.

### Answering key clinical questions

Phenotype of SRS and related imprinting disorders associated with short stature:

- Can deep phenotyping find genetic causes for specific features, such as feeding difficulties, changing appetite, poor pubertal growth spurt with rapid bone age progression, abnormal body composition, insulin resistance, and gonadal dysfunction?
- What is the contribution of genomic imprinting to growth retardation, appetite, metabolism, puberty, reproductive function, and cognitive development?
- Does imprinting affect the hypothalamic regulation of appetite/satiety?
- Why do early adrenarche and rapidly evolving puberty occur?
- GH-IGF-1 axis studies to evaluate receptor functionality and signaling to explain why is serum IGF-1 often high?
- What causes testicular dysfunction in males with 11p15 LOM?
- What are the phenotypic consequences of multi-locus imprinting disturbances?
- Why do children with UPD(7)mat have more psychiatric problems than those with 11p15 LOM?
- What are the key clinical and developmental features and/ or biomarkers pointing to a growth-related imprinting disorder?

Effect of age:

- Why does appetite change with increasing age/across the life course?

- Why are some clinical features age-specific?

Pregnancy and fertility:

- Why is the rate of children born after assisted reproductive technologies higher amongst patients with imprinting disorders and SRS than in the general population?
- Does LOM affect gametes?
- Why do fetuses with SRS and related imprinting disorders associated with short stature have small placentas?
- What is the role of IGF-2 in the growth restriction in imprinting disorders related to short stature?

Treatment:

- What is the impact of GH therapy on body composition, glucose/insulin regulation and lipid metabolism, cognition and health-related quality of life during and after treatment?
- Why do many children with SRS and associated imprinting disorders have high serum IGF-1 levels before the start of GH therapy and very high levels during therapy?
- Which treatment can preserve growth potential when there is early adrenarche and rapidly progressing puberty?
- What is the optimal treatment for imprinting disorders other than SRS, for example GH in Temple syndrome?
- How can we best develop personalized therapeutic regimens?
- Develop new and more accurate biomarkers of longitudinal growth, which can be used to assess treatment efficacy and accurately predict responses to growth-promoting therapy.

**Long-term health throughout the lifespan**

Determine the long-term consequences of SRS and related imprinting disorders on:

- Cognition, vitality, health-related quality of life, education, work, socioeconomic status, relationships and offspring.
- Cardiovascular health, glucose/insulin regulation and lipid metabolism.
- Body composition (fat mass, lean body mass, visceral fat).
- Bone density and joints.
- Reproductive function.
- Treatment, including positive, and negative effects.

Study the degree, reasons and consequences of disparities, and perform research that aims to reduce disparities, in Europe and beyond.

### Anticipated impact of future research

Establishing databases, animal models, and a biobank, as well as the application of high-throughput, omic-based methods, will not only improve the diagnostic algorithm and yield, but also increase our understanding of disturbed genomic imprinting and epigenetic regulation in general. Altogether, these strategies will lead to the identification of diagnostic/prognostic biomarkers, improvement of current treatment, development of novel and personalized therapies, and improvement and development of guidelines.

Inclusion of artificial intelligence–based diagnostic workflows and predictive methods will facilitate cost-effective decisions regarding the most appropriate treatment. Evaluation of the impact of these improvements on the care, health, and quality of life of patients and their families will help to introduce procedures preventing deterioration of mental health, thus preventing high societal costs. A greater appreciation of the natural history of these conditions will help the design of life-long health surveillance strategies.

Additionally, studying SRS might also give insights into metabolic consequences related to SGA in general, of relevance to a much larger population than just patients with SRS. Such new insights have the potential to influence wider healthcare decisions for this population born SGA and reduce healthcare costs.

## Prader-Willi syndrome

### Epidemiology, societal impact, research state of art

Prader-Willi syndrome is a rare genetic neurodevelopmental disorder due to loss of expression of paternally expressed genes in the chromosome region 15q11-q13 (OMIM #176270), due to paternal deletion of the chromosomal region (55%-60%), maternal disomy (40%-45%), imprinting mutations or epimutations (2%-5%)[26] or chromosomal rearrangements including the PWS chromosomal region. Diagnosis is ideally in the first few months of life. Incidence is approximately 1/15 000-1/25 000 live births per year.[27]

The syndrome is characterized by a specific trajectory including neurodevelopmental, nutritional, endocrine/metabolic, and behavioral dimensions, due to impaired hypothalamic development. At birth, neonates display severe muscular hypotonia with feeding difficulties. This is then followed by reduced calorie requirement, excessive weight gain, and early severe obesity with hyperphagia and poor satiety.[28] Hypothalamic impairment may lead to hormone deficiencies,[29,30] such as GH deficiency, hypogonadism, hypothyroidism, and impaired insulin secretion. Prader-Willi syndrome is the only genetic obesity with elevated ghrelin levels at all ages,[31-33] and poor muscle mass as well as high fat mass with low visceral fat. Short stature is common. Dysautonomia is also frequently observed, together with multiple comorbidities (orthopedic and ocular problems).

People with PWS display mild or moderate learning disabilities, speech and communication disorders, social disabilities, difficulties with emotional control leading to temper tantrums, compulsive and ritualistic behaviors, skin picking, and some features of autism spectrum disorder.[34-36]

This is a complex and severe condition, with high morbidity and mortality, that has large impact on the person, the family, the carers, and society.[37,38] Recombinant human GH was licensed in 2002 and improves body composition and growth, but treatment for other features of PWS does not exist. Treatment should target obesity, hyperphagia, impaired satiety, anxiety, and behavior. This requires further efforts to disentangle the mechanisms and pathophysiology of the condition, as well as to understand the specific needs of people living with PWS at all ages.

### Future research priorities

**Genetics and genomics**

- Identify the full genetic variation in the PWS locus to establish the role of genes and non-protein coding RNAs and their individual and combined contribution to the PWS phenotypes.

- Expand genetic profiling beyond the PWS locus to uncover complex gene-network effects: genome-wide methods such as genome-wide association studies and whole-genome sequencing could help define phenotypic variability and its dependence on genetic factors outside chromosome 15.
- Use larger cohorts to probe the genotype-phenotype relationships of PWS genetic subtypes extensively.
- Define the epigenetic landscape of the PWS locus at different stages of the disease and across tissues, particularly in brain and placenta. Expand the epigenetic profiling of PWS beyond methylation to also include histone modification and chromatin topology.
- Understand the interplay between environment and PWS epigenetic marks and how it might contribute to the development of features of PWS.
- Evaluate the feasibility and efficacy of incorporating PWS screening into existing prenatal screening protocols across different countries (eg, non-invasive prenatal testing), as well as developing novel, minimally invasive and cost-effective newborn screening assays for PWS.

**Animal models, iPSC, and pathophysiological research**

- Maximize the utility of iPSC and CRISPR/Cas9-engineered cellular models of PWS to decipher precise effects of genomic variance in the disease. It will be informative to expand the types of neuronal and non-neuronal differentiation models and employ organ-on-chip and 3D organoid technologies.
- Continue to develop animal models (eg, by deleting multiple PWS genes or by studying species that are closer to humans) that would display symptoms that are of primary importance to PWS, particularly hyperphagia. None of the mice models recapitulate all the symptoms observed in patients with PWS.
- Determine whether the postnatal and peripubertal periods can be used as critical windows for interventions with lasting behavioral effects, by modification of the natural trajectory.
- Understand what drives the abnormal development of hypothalamic and extra-hypothalamic circuits involved in appetite regulation in PWS.

**Biomarkers**

- Use additional omics technologies, such as metabolomics and lipidomics, to identify known and potentially further PWS subtypes, and biomarkers for their detection.
- Identify biomarkers and use AI to predict lasting effects of early treatment or intervention.
- Use functional brain magnetic resonance imaging to find targets to treat hyperphagia.
- Expand biobanking of post-mortem tissues, including placenta and fetal brains.

**Clinical issues and endocrine abnormalities**

- Unravel the mechanism of excessive fat mass with decreased lean mass, and assess the roles of oxytocin, GH, IGF-1, and insulin.
- Understand the mechanism of dysautonomia and the role of oxytocin.
- Elucidate the mechanism of the increased GH sensitivity and the roles of IGF-binding protein-7 (IGFBP-7) and IGFBP-3.
- Find the optimal treatment in poorly controlled type 2 diabetes.
- Unravel the mechanism of rapidly evolving early pubarche and develop adequate treatment.
- Understand the mechanism of combined (central and gonadal) hypogonadism in both men and women, and identify a marker for fertility in women.
- Identify the optimal treatment regimen to induce and progress puberty and maintain optimal testosterone concentrations during adulthood.
- Assess quality of life and psychological and physical well-being, for example social relationships, working capacity, fatigue, in treated and untreated people with PWS during the life span.
- Develop new and more accurate biomarkers of response to therapy, which can be used to assess treatment efficacy and accurately predict responses to therapy.
- Study the degree, reasons and consequences of disparities, and perform research that aims to reduce disparities, in Europe and beyond

**Transition of adolescents to young adults**

- Undertake research to optimize care through transition from pediatric to adult endocrinology and nutrition departments.
- Assess the long-term effects of GH treatment on body composition, and the safety and economic value of GH treatment in adolescents and adults.
- Better characterize the needs of adolescents and adults with PWS to optimize socialization, self-determination, and daily living.
- Investigate how to optimize the quality of life of people with PWS, for example by improving their environment.

**Behavioral and psychiatric issues**

- Determine genetic risk factors for psychosis.
- Understand the pathophysiology of compulsivity/impulsivity including skin picking, thinking rigidity, and social disabilities.
- Understand the biological substrates underlying the switch in feeding behavior and the specifics of PWS hyperphagia.

**Clinical trials**

- Use pharmacogenomics to understand the lack of reduction of hyperphagia in previous trials in PWS versus other conditions with hyperphagia.
- Develop early treatment with disease-modifier effects (eg, drug/interventions with epigenetic effects).
- Develop and support trials with innovative treatments for children and adults with PWS.

**Aging**

- Investigate brain anatomy and function in longitudinal studies from adolescence to late adulthood.

- Understand the mechanisms of accelerated biological aging (role of telomere length, GH treatment, and genotype) and develop potential methods for intervention.
- Develop and test tools to evaluate cognitive impairment in adults with PWS.

### Anticipated impact of the research

Developing animal models that replicate the natural history of the syndrome, establishing extensive clinical databases with lifetime information, and creating biobanks to identify new biomarkers, along with using high-throughput omic techniques, will have multiple benefits. Not only will these developments improve early diagnostic algorithms and outcomes, they will also enhance our understanding of the syndrome's natural progression (trajectory) and, in particular, the links between endocrine, metabolic, and behavioral difficulties, and lead to new approaches and therapies, including critical periods and disease-modifying drugs.

Incorporating AI-based diagnostic workflows and predictive methods will enable cost-effective treatment decisions. Evaluating the impact of these advancements on care, health, and quality of life for patients and their families will help implement effective procedures to prevent cognitive decline and reduce significant societal and public costs. A deeper understanding of the natural course of these conditions will guide lifelong health-monitoring strategies.

## Noonan syndrome

### Epidemiology, societal impact, research state of art

Noonan syndrome (OMIM #163950) is a relatively common developmental disorder with an estimated incidence of 1/2000 to 1/2500 live births per year.[39,40] The phenotype varies in severity and can affect multiple organ systems. Major features include a distinctive facial gestalt, cardiac defects (ie, pulmonary valve stenosis and hypertrophic cardiomyopathy), short stature, skeletal abnormalities (ie, pectus deformities and scoliosis), variable cognitive deficits, and predisposition to certain cancers.

In addition to the classic clinical features of Noonan syndrome, new important endocrine aspects have been reported in recent years, including metabolic abnormalities (glucose intolerance/insulin resistance, and low high-density lipoprotein) and reduced bone mass.[9,41-43] Gonadal dysfunction with deficient spermatogenesis has been reported in men with Noonan syndrome,[44,45] while fertility in women appears less affected. Very few data are available about the quality of life of either children or adults.[46]

Recombinant human GH was approved by the US Food and Drug Administration in 2007 and the European Medicines Agency in 2020 as a treatment for short children with Noonan syndrome. Although studies have shown an increase in height without serious side effects in the medium term,[47] there are still unanswered questions.

Noonan syndrome belongs to a group of phenotypically overlapping genetic disorders, including Noonan syndrome with multiple lentigines, Mazzanti syndrome (also known as Noonan syndrome-like disorder with loose anagen hair), cardio-facio-cutaneous syndrome, Costello syndrome, neurofibromatosis type 1, Legius syndrome and other emerging disorders.[48] All of these syndromes are caused by germline pathogenic variants in genes encoding components of the RAS/mitogen-activated protein kinase (MAPK) signaling pathway.[49,50] This family of disorders is known as RASopathies and is one of the largest groups of multiple congenital anomaly disorders.

A better understanding of the molecular mechanisms underlying the different manifestations of Noonan syndrome and RASopathies has led to the identification of molecular targets for specific pharmacological interventions.[51] Many specific agents (eg, SHP2 and MEK inhibitors) have already been developed for the treatment of RAS/MAPK-driven malignancies. In addition, other molecules with the property of modulating RAS/MAPK activation are indicated in non-malignant diseases (eg, C-type natriuretic peptide analogs in achondroplasia or statins in hypercholesterolemia), and may offer opportunities to develop target treatment for RASopathies.

### Future research priorities

#### Molecular bases and genotype-phenotype correlations

- Identify the missing genes responsible for Noonan syndrome and other RASopathies or alternative diagnoses for individuals presenting with RASopathy-like phenotypes.
- Expand knowledge of clinically relevant genotype-phenotype correlations at both gene and variant levels.
- Develop Noonan syndrome-specific growth charts according to the genotype. Assess whether the origin of short stature may vary among different genotypes (eg, GH secretion pattern and partial GH insensitivity, as well as defective chondrocyte differentiation).[52,53]
- Develop in vitro and in vivo model systems to understand pathogenetic mechanisms, and develop functional assays to characterize the impact of genetic variants.

#### Natural history and long-term health throughout the lifespan

Although the course of the disease is well known in childhood, there is still very limited information available about the natural history of Noonan syndrome in adulthood. An important challenge is to better describe the outcome in adulthood, particularly in terms of fertility, bone health, and possible metabolic dysfunction.

- Expand studies of health-related quality of life as little is known in people with Noonan syndrome.[46]
- Carry out prospective studies to investigate the prevalence and mechanisms of infertility in both men and women. Gonadal dysfunction with deficient spermatogenesis has been reported in men with Noonan syndrome.[44,45]
- Investigate bone mass accrual and assessment of bone fragility in adults and the elderly. Decreased bone mass has been reported in Noonan syndrome and in other RASopathies.[43,54]
- Perform prospective long-term follow-up studies to further investigate a possible risk of type 2 diabetes or other metabolic disturbances.
- Perform collaborative research into the pathophysiology and management of bleeding disorder and risk of malignancies in several subtypes of Noonan syndrome and other RASopathies.
- Assess psychological and physical wellbeing, for example social relationships, working capacity, fatigue, in treated and untreated people with Noonan syndrome during the life span.

- Study the degree, reasons and consequences of disparities, and perform research that aims to reduce disparities, in Europe and beyond

#### Current and future therapeutic perspectives

- Address the following unresolved issues regarding GH treatment:
  - Differential response to therapy by genotype.
  - Potential beneficial effects on muscle hypotonia and motor development.
  - Safety in patients with pre-existing hypertrophic cardiomyopathy.
  - Safety regarding tumor risk.
  - Final adult height and the actual gain in height, using controlled trials that take into consideration the late growth due to late puberty.
  - Develop new and more accurate biomarkers of longitudinal growth, which can be used to assess treatment efficacy and accurately predict responses to growth-promoting therapy.
- Examine future therapeutic perspectives:
  - Drug repurposing of compounds modulating RAS/MAPK activation as a new approach to treat or prevent medical complications associated with RASopathies.
  - Other potential targets for selective therapies, such as correction of functional defects at the subcellular, cellular, or tissue levels (ie, dysfunction of the myelomonocytic lineage or mitochondrial bioenergetics).

### Anticipated impact of future research

The development of national and international registries would be valuable to collect data on the natural history of these patients, including the medical complications that may arise during their lifetime, and to assess the efficacy and safety of specific medical interventions. A better understanding of the disease will help to establish evidence-based recommendations for the management of patients with Noonan syndrome, and may lead to the identification of drug targets and the development of therapy.

## Tall stature

### Epidemiology, societal impact, research state of art

Tall stature syndromes encompass the family of OGID syndromes, characterized by increased height with or without increased head circumference, in association with an intellectual disability[15] and tall stature without an intellectual disability.

The OGID syndromes are rare, and prevalence is not accurately known. Several monogenic causes of the OGID syndromes have been identified, including *NSD1* (Sotos syndrome, OMIM #117550), *NFIX* (Malan syndrome, OMIM #614753), *EZH2* (Weaver syndrome, OMIM #277590), *DNMT3A* (Tatton-Brown-Rahman syndrome, OMIM #615879), *PTEN* (PTEN hamartoma tumor syndrome, OMIM #601728), *CHD8* (OMIM #615032), *GPC3* (Simpson-Golabi-Behmel syndrome, OMIM #312870) and *MTOR* (Smith-Kingsmore syndrome, OMIM #616638). While each condition is characterized by a unique phenotype and often recognizable facial gestalt, differentiation can be challenging and requires genetic investigation.[55,56]

There is societal impact of these conditions, as they are complex multi-organ syndromes that affect physical health and require lifelong multi-disciplinary medical input for assessment and treatment of complications. People with OGID syndromes are often not able to work and require lifelong support from others.

Tall stature syndromes without learning difficulties encompass a variety of conditions. Marfan syndrome (OMIM #154700), caused by a pathogenic variant in the *FBN1* gene, is the most common (prevalence approximately 1/5000).[16] Phenotypically related conditions are those due to variants of genes encoding components of the transforming growth factor-β (TGFβ) signaling pathway, notably the *TGFβR1* and *TGFβR2* genes, such as Loeys-Dietz syndromes (OMIM #609192 and #610168),[57] and other tall stature syndromes without learning disabilities exist. Familial tall stature may have monogenic or polygenic genetic causes and is often not further investigated.

Marfan syndrome affects multiple organs and tissues, including the cardiovascular (ie, mitral valve prolapse, aortic root aneurysm and dissection), ocular (ie, severe myopia and ectopia lentis) and skeletal (ie, disproportionately tall stature, arachnodactyly, pectus deformity, and scoliosis) systems.[16] With the advances in the diagnosis and management of life-threatening cardiovascular events that have occurred over the past 50 years, individuals with Marfan syndrome currently have a life expectancy approaching that of the general population.[58] However, patients with Marfan syndrome continue to face many morbidities, including the sequelae of multiple surgeries, as well as musculoskeletal impairments.

Health-related quality of life in MSF is highly correlated with musculoskeletal defects, aerobic capacity, and physical deconditioning,[59] but little is known about psychosocial functioning. Due to their rarity, little is known of the natural history and consequences of most other syndromic and non-syndromic tall stature conditions on health and well-being in today's society.

Tall stature syndromes are often diagnosed late after a long diagnostic odyssey. Earlier diagnosis will allow for earlier appropriate management,[56] for example screening for aorta pathology in Marfan syndrome.

There are limited pharmacological options to inhibit growth, and no drugs are licensed. Knowledge of signaling pathways for growth is expanding, and pharmacological targets have been identified, but drugs with high efficacy and long-term safety have yet to be developed.

### Future research priorities

The main aim for future research is to develop personalized medicine, determined by the underlying gene variant, leading to gene-directed therapy and surveillance for tall stature syndromes (with or without intellectual disability). To achieve this aim, the following topics and research questions need to be addressed.

#### Molecular bases and genotype-phenotype correlations

- Identify new genes or new genetic/epigenetic mechanisms for tall stature syndromes, by genetic investigations of patients with a tall stature syndrome and healthy families with extreme tall stature.
- Use methylation signatures to discover new genes involved in tall stature syndromes.
- Investigate genotype-phenotype correlations to determine whether syndrome information (including prognosis) and

management guidance should be variant rather than gene based.
- Understand the biological mechanisms that result in aberrant growth and tall stature, at both cellular level and organ level, including the growth plate.

**Natural history and long-term health throughout the lifespan**

- Clarify and expand (where appropriate) the phenotype of tall stature syndromes, including longitudinal studies to determine adult phenotype.
- Assess the natural history and long-term health consequences of OGID and non-syndromic tall stature in adulthood, including quality of life and psychosocial functioning.
- Study the degree, reasons and consequences of disparities, and perform research that aims to reduce disparities, in Europe and beyond

**Therapeutic perspectives**

- Develop new therapies for the treatment of monogenic tall stature syndromes, including:
  - use of molecular targets for specific pharmacological interventions, with development of drug trials (ie, TGFβ pathway inhibitors or modulators).
  - identification of new molecular targets and drugs for inhibition of growth.

- Translate knowledge of mechanisms of tall stature into drugs for treatment of short stature.
- Further investigate the use of epiphysiodesis for tall stature (eg, outcomes, complications, optimal age).
- Develop new and more accurate biomarkers of longitudinal growth, which can be used to assess treatment efficacy and accurately predict responses to therapy.

**Clinical care**

- Enable earlier recognition and diagnosis of OGID syndromes.
- Develop specific management guidelines (including for surveillance), based on the evolving phenotypic understanding and genotype-phenotype correlations.

## Anticipated impact of future research

Earlier diagnosis will allow for earlier appropriate management: for example, early screening for aorta pathology in Marfan syndrome, or screening for intellectual disability and/or associated medical complications (including, for some, an increased tumor risk) in OGID syndromes.

The better understanding of the molecular mechanisms underlying the different manifestations of tall stature syndromes will help to identify molecular targets for specific pharmacological interventions. Pharmacological intervention may improve the quality of life of these patients. Knowing about the long-term psychological and physical well-being of these groups of patients will allow for improvement in supporting them from medical and psychological points of view.

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## Authors' contributions

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