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Review Article

Growth hormone therapy in children; research and practice – A review

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ABSTRACT

Short stature remains the most common reason for referral to a pediatric Endocrinologist and its management remains a challenge. One of the main controversies is the diagnosis of idiopathic short stature and the role of new technologies for genetic investigation of children with inadequate growth.

Complexities in management of children with short stature includes selection of who should receive interventions such as recombinant human growth hormone, and how should this agent dose be adjusted during treatment. Should anthropometrical data be the primary determinant or should biochemical and genetic data be used to improve growth response and safety? Furthermore, what is considered a suboptimal response to growth hormone therapy and how should this be managed?

Treatment of children with short stature remains a "hot" topic and more data is needed in several areas. These issues are reviewed in this paper.

1. The importance of anthropometric data in Pediatrics

Height follows a normal distribution in a given population, depending upon age and gender, therefore, by definition, 2.3% and 0.6% of healthy individuals have height that falls 2 and 2.5 standard deviations below the median height-for-age of the reference population, respectively [1,2]. However conditions that cause a negative long-term effect on children's health decrease the growth rate leading to short stature. The height distribution observed within a group of patients with similar pathological conditions also presents with a normal distribution, but with mean values lower than the reference population [3–7]. Thus, it is expected that there will be a progressively higher incidence of individuals with defined pathology among children with a lower standard deviation score (SDS) of height. Based on these premises, several studies demonstrated that height evaluation is an important tool to monitor the health status of children [8].

2. Criteria for investigation of children with a complaint of short stature

A number of conditions can manifest with growth attenuation and/or short stature [2–7] (Table 1). In several of them, the growth disorder

Abbreviations: BMI, Body mass index; GH, Growth hormone; GHD, Growth hormone deficiency; IGHD, Isolated Growth hormone deficiency; MPHD, Multiple pituitary hormone deficiencies; rhGH, recombinant human growth hormone; IGF-I, Insulin-like growth factor; SD, Standard deviation; SDS, Standard deviation scores; SGA, Small for gestational age; SH, Sitting height

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Table 1
Main identified causes of short stature.

	Estimated frequency
Isolated short stature (former designated as "normal variants of growth")	> 60%
• ISS	
• Familial Short stature	
• Constitutional delay of growth and puberty (CDGP)	
Children born SGA	~2%
Turner syndrome	~2% of females
Syndromic short stature	~5%
• Noonan syndrome	
• Neurofibromatosis type 1	
• Silver-Russell syndrome	
• Prader-Willi syndrome	
• CHARGE syndrome	
• Bloom syndrome	
• Fanconi Anemia	
• Three-M syndrome	
Disorders of the GH/IGF axis	~2%
• Growth hormone deficiency	
• Bioinactive GH (Kowarski syndrome)	
• GH Insensitivity (*GHR*, *STAT5B*)	
• Ternary complex defects (*IGFALS*, *PAPPA2*)	
• IGFs deficiency (*IGF1*, *IGF2*)	
• Bio-inactive IGF-1	
• IGFs insensitivity (*IGF1R*)	
Skeletal dysplasia	~2%
• Achondroplasia	
• Hypochondroplasia	
Chronic systemic diseases	~2%
• Primary and secondary undernutrition	
• Chronic kidney disease (renal failure, tubular acidosis, nephrotic syndrome)	
• Gastrointestinal disease (intestinal inflammatory disease)	
• Rheumatologic disease (especially systemic juvenile idiopathic arthritis)	
• Hematological (chronic anemia)	
• Cardiac disease	
• Pulmonary disease (cystic fibrosis)	
• Muscular and neurological disorders, *e.g.* congenital myotonia	
• Endocrine (hypercortisolism, rickets)	
Primary hypothyroidism	< 1%
Celiac disease	< 1%
Psychosocial deprivation	< 1%

may be the primary or sole manifestation. All children should have their growth monitored by regular measurement of height/length and weight with the aim of early recognition of these conditions. Accurate height measurement using a wall stadiometer is essential, [2] as is the use of validated growth curves [9–12]. There is considerable debate about the use of international or local growth curves. In general, the use of validated specific population curves is desired as this improves the accuracy of the use of height measurements as a tool to identify health problems and minimize unnecessary investigations [12,13,14]. Additionally, using the height of the parents plotted on the same growth curve may help to define an expected growth pattern for a particular family [15,16].

Criteria adopted to refer a child for a short stature investigation vary in terms of sensitivity, specificity and complexity (Fig. 1). The more severe the short stature the greater the probability that it is caused by a pathological condition and that it is not a normal variant of growth. Even though short stature can be defined as a height > 2 SDS below the mean for a given age and gender (or below the mean parental height SDS), in the absence of other symptoms and signs, the large majority of short statured children are in fact healthy [14]. The use of more restricted referral criteria or associations of other clinical findings are frequently used to improve the identification of pathological conditions and reduce unnecessary investigations [17,18] (Fig. 1). The presence of short stature in relation to the parental height (target height), decreased growth velocity and deflection in the growth curve are anthropometric signs that indicate a higher probability of pathologic conditions affecting growth [19]. The presence of dysmorphic features, body disproportion or symptoms/signs of specific diseases significantly increase the probability that short stature is caused by a specific pathologic cause requiring prompt investigation [18].

3. Differential diagnoses of short stature

Short stature can be the first and/or main symptom of numerous conditions and diseases (Table 1) [7] and this makes it very challenging to establish the precise diagnosis. From a practical point of view, short children may be classified into three different main groups (Fig. 2): children with signs or symptoms of specific conditions that cause chronic disease; children with major clinical findings that indicate a syndromic condition (in general with a genetic basis) and finally apparently healthy (asymptomatic) children with isolated short stature.

When it comes to categorization of children with short stature in relation to the cause for the short stature, the classical approach has been to divide them in two main groups [2,20]: the first group comprises children with short stature caused by unknown mechanisms and the second group is composed of children affected by recognizable conditions resulting in growth disturbance. These pathological conditions can be further classified according to the mechanism that causes short stature: in primary short stature which comprises defects in growth plate; and in secondary short stature which includes a heterogeneous group of chronic conditions.

The number of known genetic conditions accounting for growth disorders has markedly increased in the last decade [21]. These diseases usually affect growth by multiple mechanisms, some of them not completely elucidated [21]. Additionally, several genes were demonstrated to be able to cause short stature without other clinical manifestations in conditions that were previously classified as normal variant of growth [22–25]. This knowledge is challenging the concept that the group of children with the diagnosis of idiopathic short stature (ISS) [20] or small for gestational age (SGA) would only contain patients without pathological conditions and that they would not need further investigation or follow-up [26,27].

The frequency of each of these conditions in a given group of patients with short stature varies depending on the population, selection criteria, referral bias and investigation approach (Table 1). As a rule, most children with height SDS < −2 will be classified as having a normal variant of growth [28,29]. Growth hormone deficiency (GHD), Turner syndrome, celiac disease and inflammatory bowel diseases are considered as priority target conditions for growth monitoring, and consequently, for investigation in short stature children [7]. All of these conditions can first be manifested as a growth disorder and have a natural history that includes a long period without specific symptoms. Because these conditions may cause serious effects on health, early diagnosis brings significant benefit to the patient [7]. Other conditions, such as cystic fibrosis, undernutrition, psychosocial deprivation, hypothyroidism and hypercortisolism should be considered in the evaluation of a child with short stature.

4. Diagnostic investigation

4.1. First step – Clinical evaluation

Despite the complexity and multiplicity of potential causes, several diagnoses can be established by a carefully elicited medical history and a comprehensive physical examination [2] (Table 2). This process aims

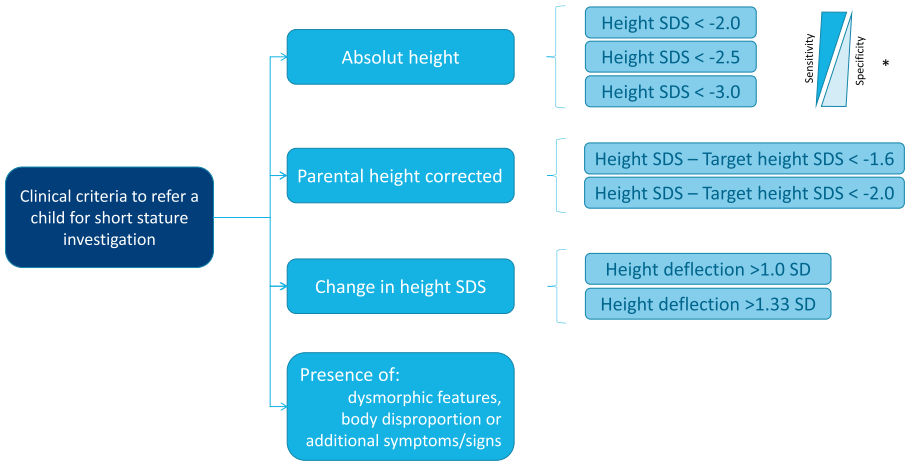

Fig. 1. Clinical criteria to refer a child for short stature investigation. * – sensitivity and specificity in relation to the possibility of identifying a pathologic conditions affecting growth.

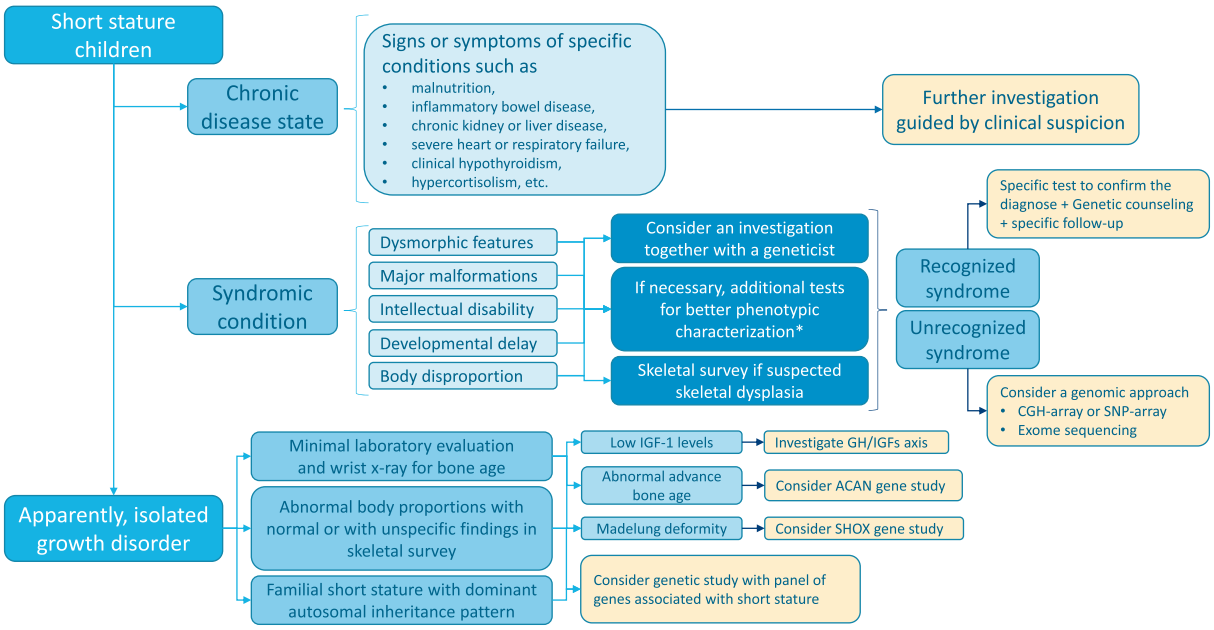

Fig. 2. Overview of the investigation of children with short stature.

to recognize the presence of signs and symptoms that indicate a specific condition causing growth failure and thus guide further investigation. During the clinical evaluation, it is usually possible to distinguish children with short stature associated with chronic disease states or with syndromic conditions from those who are apparently healthy (Fig. 2).

A key point is a detailed description of the child's growth pattern, including the time when the growth deficit was first observed. Birth characteristics must be evaluated (gestation and delivery conditions or complications; gestational age, birth weight, length and head circumference), assessing if the growth impairment had a prenatal or postnatal onset. Medical history must be assessed, with a focus on neuropsychomotor development, nutritional status, medication use, and cardiac, renal, pulmonary, neurologic and gastrointestinal symptoms/complaints [2,30].

Physical examination should include the description of anthropometric measurements, dysmorphic features, and any other clues for one of the many causes of short stature (Table 2). In children younger than 2–3 years of age, supine length, weight, weight-for-length, and head circumference should be measured, and fontanelles as well as dentition should be evaluated. In older children, erect height, arm span, sitting height (SH), head circumference and weight should be measured [2]. Body mass index (BMI) and sitting height:height ratio (SH:H) should be calculated. The pubertal status should be assessed. Evaluation of a child's height must be done in the context of standards for sex and age. Such standards can be either cross-sectional (by calculation of height SDS) or longitudinal (by plotting in growth charts). Serial measurements with a minimum interval of 6 months are necessary to determine the height velocity. Because genetic factors are important determinants of growth and height, sibling and parental height and pubertal pattern should be noted.

Many abnormal growth states are characterized by disproportionate growth, which is suggestive of skeletal dysplasia. Therefore, body proportion measurements should be part of the evaluation of short stature. The use of SH:H for age and sex, which can also be expressed in SDS, according to published standards [31] allows for the observation of body proportion changes throughout development. Children with short stature and an increased SH:H ratio for age and sex have a disproportional short stature caused by limb abnormalities, while children with short stature and a decreased SH:H ratio for age and sex have a

Table 2
Specific diagnostic findings and key points in medical history and physical examination of children with short stature.

Findings and key points	Interpretation and application
Medical history	
Birth length, weight, head circumference, gestational age	Classification as SGA or AGA
Previous growth data	Height velocity and growth pattern analysis
Age at start of pubertal signs	Early, normal, or delayed puberty
Previous diseases, surgeries, and medication use (special attention to the use of glucocorticoids)	To identify organic or iatrogenic causes
Medical history of the various systems	To identify chronic and systemic diseases
Feeding and nutrition history	To identify states of malnutrition or child neglect
Neuropsychomotor development delay and/or intellectual disability	Syndromes, chromosomal disorders, metabolic disorders
Family history of similar cases, consanguinity or family from isolated community families. Draw the family pedigree.	To identify monogenic disorders with autossomic dominant or recessive inheritance
Parental height (measured)	To estimate the target height
Parents' age at the start of puberty	To assess likelihood of a familiar pattern of delayed puberty
Physical examination	
Length or height SDS	To assess the severity of growth deficit
Body proportions (sitting height:total height ratio SDS; arm spam)	To identify altered sitting height:height ratio as a suggestive sign of skeletal dysplasia
Weight-for-height or BMI showing underweight	Weight more affected than height, low weight-for-height and low BMI are suggestive of malnutrition
Weight-for-height or BMI showing overweight or obesity	Hypothyroidism, Cushing's syndrome, GH deficiency, pseudohypoparathyroidism
Head circumference SDS	Microcephaly and macrocephaly are important findings, indicating potential diagnosis
Dysmorphic features	Syndromes
Pubertal stage	Early, normal or delayed puberty
General physical exam	Search for chronic and systemic diseases

SGA Small for gestational age, AGA Adequate for gestational age, BMI Body mass index, GH Growth hormone.

disproportional short stature caused by axial segment abnormalities [24].

4.2. Second step – Diagnostic testing

Depending on specific clinical findings from the medical history and physical examination, special investigations are required to confirm the initial clinical impression. When a skeletal dysplasia is suspected, mainly for children with body disproportion abnormalities or skeletal deformities, skeletal survey analysis, including skull, spine, pelvis, upper and lower limbs, should be obtained for a more precise diagnosis [32]. Likewise, when dysmorphic features are suggestive of syndromic causes, diagnostic investigations should prioritize those possibilities. When a specific syndrome is recognized by clinical evaluation, the patient should be specifically tested. On the other hand, if no syndrome is clinically recognizable, patients with short stature associated with dysmorphic features should undergo genetic testing, including molecular karyotyping (single nucleotide polymorphism (SNP) array or array-comparative genomic hybridization (CGH) [33] and/or whole-genome sequencing [34,35]. In this scenario, it is important to consider referring to a geneticist, dysmorphologist and/or pediatric endocrinologist group specializing in growth disorders for a more detailed evaluation.

The majority of short children evaluated for short stature are apparently healthy and their medical history and physical examination do not bring any specific clue to guide further laboratory or imaging exams. Fewer than 1% of short apparently healthy children will have a pathologic condition [29]. In patients with a low pretest probability of disease, one must be careful regarding the interpretation of any abnormal test. The diagnostic workup should include tests for a group of diseases that can be associated with short stature with minimal other signs and symptoms [5,17].

Most clinicians consider a radiograph of the left hand and wrist (to assess the bone age) a useful test. There are two main standards to evaluate the bone age: Greulich and Pyle [36] and Tanner-Whitehouse [37]. The most commonly used method for height prediction based on bone age is the Bayley and Pinneau method [38]. More recently an automated method to determine skeletal maturity became available [39]. This new methodology decreases the variability so common in manual methods of bone age assessment. Advanced bone age in relation to chronological age, especially in prepubertal children, suggest defects in the *ACAN* gene [40]. Mild and nonspecific findings on hand and wrist x-ray, such as short metacarpals or short middle phalanges, can suggest defects in genes involved in growth plate maturation (*GNAS, NPR2, NPPC* and *IHH*) [23–25]. Even though most conditions that affect growth cause bone age delay, the most common cause of delayed bone age is constitutional.

There are few evidence-base studies that support a list of minimal laboratory evaluations that should be systematically performed in all children with short stature [29,41]. In an apparently healthy short child, the laboratory tests could include serum concentrations of IGF-1, TSH/Free T4 and initial screening tests for celiac disease [2,29,30,41]. IGFBP-3 measurement in children younger than 3 years of age may improve the assessment of the GH/IGF-1 axis [42]. In childhood survivors of neoplasias, particularly those who received cranial radiotherapy, the accuracy of serum levels of IGF-I/IGFBP-3 is decreased [43]. Blood count, C-reactive protein and erythrocyte sedimentation rate can help to detect inflammatory states. It is a common practice to also include renal function tests and liver function tests in the evaluation. Additionally, it is generally advised to request a conventional or molecular (SNP array or array CGH) karyotype for short girls, even in the absence of typical signs of Turner syndrome [44]. The inclusion of additional laboratory tests increases the cost of the investigation, and one should be aware that there is a relatively low probability of establishing a pathologic diagnosis in asymptomatic short children [29].

Defects of GH/IGF-1 axis should be investigated in patients with suggestive clinical findings. This is a heterogeneous group of conditions with a distinct phenotype (Table 3) [21,45]. GHD is by far the most common defect in the GH/IGF-1 axis [8], although its frequency is only 1–2% in a non-selected group of short stature children. More recently, it was suggested that *IGF1R* defects leading to variable degree of IGF-1 insensitivity can be present in 2% of children born SGA and without catch-up growth [46]. Longstanding short stature caused by GHD (except in the presence of precocious puberty) is accompanied by at least 1–2 years delay in bone age, and therefore, children older than 3 years with a bone age equal to or above chronological age should not be investigated for GHD [47,48]. The determination of IGF-1 levels is usually the first step to assess GH/IGF-1 axis [49] (Fig. 3). Children with IGF-1 serum levels above the mean for age and gender are unlikely to have defects in the GH/IGF axis [47] except for IGF-1 insensitivity

Table 3
Disorders of the GH/IGF axis associated with short stature.

GH deficiency
• Idiopathic
• Acquired (craniopharyngioma, pituitary tumors, autoimmune diseases, granulomatous diseases, central nervous system infections, post-radiotherapy, head trauma)
• Congenital: associated with structural defects
• Genetic
o GH secretion (*GH1* and *GHRHR* genes)
o Pituitary cells differentiation (*POU1F1* and *PROP1* genes)
o Pituitary development (*HESX1, GLI2, OTX2, LHX3, LHX4*, and *SOX3* genes)
Bioinactive GH (Kowarski syndrome, OMIM 262650)
GH Insensitivity (GHI)
• Complete GHI (OMIM 262500)
• Partial GHI (OMIM 604271)
• GHI associated to immune dysfunction (OMIM 245590)
• Atypical GHI
• Secondary or acquired GHI (Anti GH antibodies, malnutrition, liver disorders, poorly controlled diabetes mellitus, uremia)
Ternary complex defects
• Acid-labile subunit deficiency (OMIM 615961)
• Defects on proteolytic cleavage of IGFBPs (*PAPPA2* gene)
IGFs deficiency
• IGF1 deficiency (OMIM 608747)
• IGF2 deficiency (OMIM 616489)
Bioinactive IGF-1
IGFs insensitivity (OMIM 270450)

GH growth hormone, *IGF-1* insulin-like growth factor type 1, *IGFBP-3* insulin-like growth factors binding protein 3, *ALS* acid-label subunit, *IGFs*, insulin-like growth factors.

and PAPPA2 deficiency [50]. Children with low / low normal serum levels of IGF-I should be further investigated for GHD.

The next step is to assess the production of GH. Since there is a physiological circadian variation in serum levels of GH, random levels are not useful, except in the neonatal period, where levels tend to be high all day [51,52]. During the first week of life, a single random GH level < 7 ng/ml confirms the diagnosis of GHD [52]. Growth hormone stimulation tests have been used for decades to measure the response of the hypothalamus/pituitary gland to various stimuli. Even though they are considered the gold standard test to diagnose GHD, there are several problems with them: (1) there is variable reproducibility, meaning that the same test in the same person on different days can give completely different results and different tests in the same individual can also produce different results. (2) there are different laboratory methods to measure GH and the results between different methods may not be similar, (3) different laboratories using the same methods find different results for the same samples and, (4) there are no agreed-upon normal cut-offs points and since different stimuli lead to different GH peaks, there may be a need for stimulus-specific cut-off points [14,42,53,54,55].

In the 1980's the cut-off point used to define GHD was 5 ng/ml, using polyclonal antibody assays. This means that if the highest GH level after a stimulus was below 5 ng/dl, the child was considered to have GHD, and if the value was above that, the child was considered not to have GHD. Later, the cut-off point was raised to 7 ng/ml and then to 10 ng/ml, and now, most assays use monoclonal antibodies that lead to varying apparent GH concentrations [53,56,57]. Raising the cut-off limit increases the number of children diagnosed with partial GHD, but it also increases the likelihood of diagnosis of GHD in children without the condition. The ideal cut-off point to identify most children with GHD without classifying non-GHD children as GHD and how to improve the accuracy of the diagnosis of GHD and non-GHD are topics still under debate [49,53].

Another issue is that adolescents, due to their exposure to sex steroids, have a higher growth hormone response to stimuli. Some clinicians suggest that all children should receive sex steroid priming prior to stimulation tests, to decrease the number of false positive diagnoses [58], while others suggest that priming should be done only for peripubertal individuals [59] or only for prepubertal children already at pubertal age (delayed puberty) [60]. However, conflicting published data show that priming induces higher values of GH levels but does not necessarily improve the accuracy of diagnosing GHD. Furthermore, sex steroid priming may not discriminate between those who are likely to have a clinically significant improvement in adult height after rhGH treatment from those who are not going to have a significant change; priming may also have side effects such as priapism and testicular pain [61]. A recent systematic review on the diagnosis of GHD as a late effect of radiotherapy reported that there are no studies evaluating the use of sex steroid priming in childhood cancer survivors [62]. The use of priming is one more tool that can be used by the Pediatric Endocrinologist in selected cases. In summary the diagnosis of GHD should be based on a combination of factors, including auxologic data (height SDS and growth velocity), radiologic data (delayed bone age, with some exceptions, and pituitary imaging), laboratory data (IGF-1/IGFBP-3 and GH stimulation tests) and clinical expertise.

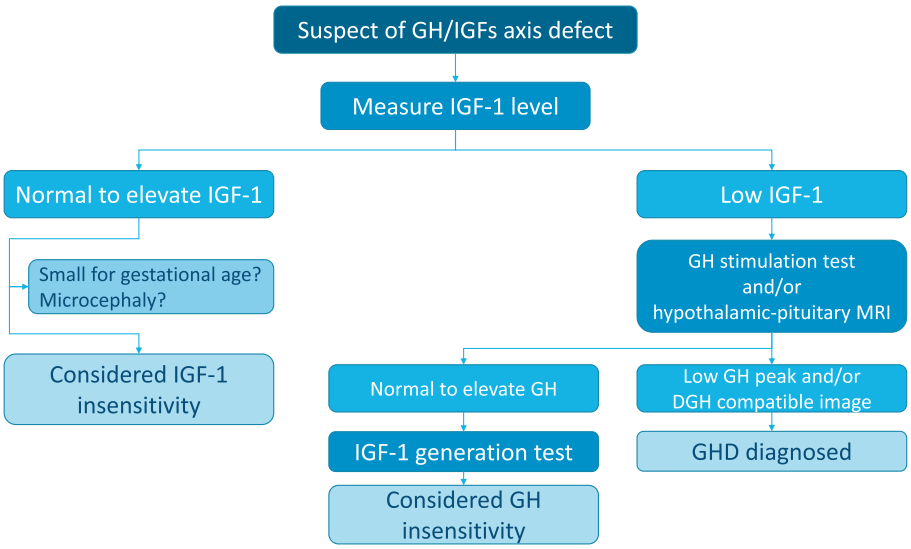

Fig. 3. Overview of the investigation of GH-IGF1 axis defects.

Table 4
Examples of genetic conditions associated with short stature organized according to their primary mechanism.

Condition	Inheritance	Gene	OMIM
Disorders of the GH/IGF axis			
See Table 4			
Associated with Skeletal dysplasia			
• Disorders affecting paracrine factors in the growth plate			
Achondroplasia	AD	*FGFR3*	100800
Hypochondroplasia	AD	*FGFR3*	146000
Acrocapitofemoral dysplasia	AR	*IHH*	607778
Albright hereditary osteodystrophy	AD	*GNAS*	103580
Acromesomelic dysplasia, Maroteaux type	AR	*NPR2*	602875
Geleophysic dysplasia 1	AR	*ADAMTSL2*	231050
• Defects affecting cartilage extracellular matrix			
Acromicric dysplasia	AD	*FBN1*	102370
Geleophysic dysplasia 2	AD	*FBN1*	614185
Pseudoachondroplasia	AD	*COMP*	177170
Spondyloepiphyseal dysplasia congenita	AD	*COL2A1*	183900
Spondyloepimetaphy-seal dysplasia aggrecan type	AR	*ACAN*	612813
Spondyloepiphyseal dysplasia type Kimberley	AD	*ACAN*	608361
• Defects affecting intracellular pathways			
Langer mesomelic dysplasia	AR	*SHOX*	249700
Leri–Weill dyschon-drosteosis	AD	*SHOX*	127300
Campomelic dysplasia	AD	*SOX9*	114290
Associated with syndromic short stature			
• Defects affecting intracellular pathways			
Noonan syndrome	AD	several	163950
Neurofibromatosis type 1	AD	*NF1*	162200
Kabuki syndrome 1	AD	*KMT2D*	147920
Kabuki syndrome 2	XLD	*KDM6A*	300867
Kenny–Caffey syndrome type 1	AR	*TBCE*	244460
Kenny-Caffey syndrome, type 2	AD	*FAM111A*	127000
• Defects in fundamental cellular processes			
Floating–Harbor syndrome	AD	*SRCAP*	136140
KBG syndrome	AD	ANKRD11	148050
CHARGE syndrome	AD	*CHD7, SEMA3E*	214800
Cornelia de Lange syndrome	AD / XLD	several	122470
Rubinstein–Taybi syndrome	AD	*CREBBP, EP300*	180849
Bloom syndrome	AR	*RECQL3*	210900
Fanconi Anemia	AR /XLR	*several*	227650
Three-M syndrome	AR	*CUL7, OBSL1, CCDC8*	273750
MOPD	AR	*RNU4ATAC, PCNT*	210710

MOPD = microcephalic osteodysplastic primordial dwarfism.

4.3. Recommendations for genetic testing in the evaluation of a child with short stature

Genetic tests are being progressively introduced into clinical practice in all fields of medicine, including the evaluation of children with short stature. There are > 1000 conditions in OMIM® data base (https://www.omim.org/) associated with short stature with a known molecular basis [21]. They can be organized as conditions involving GH/IGF defects (Table 3), conditions causing skeletal dysplasia (reviewed in [63]) or conditions associated with syndromic presentations (Table 4). The diagnosis of several of these conditions can be made based on clinical and complementary exams (Fig. 2) [21,34,64,65], with genetic testing serving to confirm the diagnosis. A candidate gene approach is used in these situations. However due to the diversity, clinical variability and rarity of these conditions, the clinical diagnosis can be challenging [66–69].

In the last decade, the development of genetic techniques, primarily array-based genomic copy number analyses (or molecular karyotype) and whole exome/genome sequencing (WES/WGS), have led to an increase in the diagnosis of patients with unrecognized rare genetic conditions [70–73]. The use of these methodologies as the first line of investigation of genetic conditions has been shown to yield a high rate of success to establish the etiological diagnosis and to be cost effective in selected situations [70,71,73,74].

In the field of growth disorders, the prevalence of pathogenic copy number variation (CNV), especially when associated with developmental delay, intellectual disability or additional major malformations, is 13% (95% confidence interval of 10.4–15.5%) [75]. Array-based CNV analyses, such as comparative genomic hybridization (aCGH) or single nucleotide polymorphism arrays (SNPa), should be used to aid in the diagnosis in these children (Fig. 2) [34,64,65].

Regarding skeletal dysplasias, it is worth highlighting the investigation of *SHOX* defects in patients and families with suspected Leri-Weill dyschondrosteosis. Heterozygous defects of the *SHOX* gene is considered the main monogenic form of short stature, most often resulting in disproportionate short stature with mesomelia (short middle segment – radius, ulna, tibia and fibula) and variable degrees of Madelung deformity [76]. Children with *SHOX* haploinsufficiency significantly benefit from rhGH therapy [77]. Since the majority of patients and families with defects in *SHOX* have deletions involving the gene and/or its regulatory region, it is important to use a sensitive methodology to identify small CNV in this target region [76].

When there is a high degree of suspicion that the short stature is due to a monogenic condition, based on the history of consanguinity, clear autosomal dominant inheritance pattern, syndromic cases and severe short stature, WES should be used. The usefulness of WES in growth disorders was demonstrated in several case reports [31,67,78], in cohorts of patients with severe short stature [79,80] and in the investigation of specific subtype of short stature children (as GHI) [81].

There are specific situations where genetic investigation gains importance due to the prevalence of the condition or due to the influence of the correct diagnosis in the treatment decision process (Table 5). As already mentioned, every girl with short stature of undetermined cause needs a conventional or molecular karyotyping due to the possibility of Turner's syndrome [43]. Additionally, genetic investigation is more relevant when there is clinical suspicion of a cancer predisposition condition, such as neurofibromatosis type 1, Noonan syndrome, Fanconi anemia or Bloom disease [69,82,83]. In typical cases, the genetic test leads to little change in the diagnostic or therapeutic approach, but for atypical or mild cases, a molecular confirmation of the diagnosis has an obvious impact on genetic counseling, decision to use rhGH therapy and patient follow up.

The sheer number of genes involved in growth disorders and the number of possible tests to investigate them is beyond the scope of this paper [84]. A limited number of examples are listed in Table 5. Public databases such as GeneReview (https://www.ncbi.nlm.nih.gov/books/NBK1116/), Genetics Home Reference (https://ghr.nlm.nih.gov/) and OMIM (https://www.omim.org/) are useful in assisting the decision-making process regarding the use of a given genetic test.

The majority of children with height SDS < −2 have isolated short stature and are labeled as ISS. In these children, the absence of other clinical signs or the presence of nonspecific findings currently makes the gene candidate approach impracticable. There are no clear recommendations for when and how to do genetic investigation in children with isolated short stature. Since height is one of the most heritable human characteristics [85] and many children with short stature have parents with short stature, it is expected that the cause of a large proportion of these children is genetic. It has been accepted that there is a polygenic influence determining short stature [86,87], but recent studies have challenged this dogma. Several studies demonstrated that a significant portion of healthy short children have a monogenic cause

Table 5
Examples of genetic tests important for short stature evaluation.

Test	Main indication	Ref.
Single gene/locus investigation		
SHOX: CNV analysis (MLPA) followed by Sanger sequencing	Suspicion of Léri-Weill dyschondrosteosis (DLW)	[95]
FGFR3: Sanger sequencing of mutation hot-spots	Suspicion of Hypochondroplasia	[96]
Evaluate methylation defects chr 11p15.5 followed by assess the presence of maternal UPD chr. 7	Suspicion of Silver-Russell syndrome	[97]
GNAS: Sanger sequencing	Suspicion of Albright hereditary osteodystrophy or Pseudohypoparathyroidism	[98]
PROP1: Sanger sequencing followed by CNV analysis (MLPA)	Combined pituitary hormone deficiency (GH, PRL, TSH, LH/FSH) with intact pituitary stalk	[99]
GH1: Sanger sequencing	Suspicion of Autosomal dominant GH deficiency	[100]
Multigene panel sequencing		
PTPN11, *SOS1*, *RAF1*. *RIT1*, and > 10 other genes	Suspicion of Noonan syndrome or overlap conditions	[101]
Panel that includes genes associated with main skeletal dysplasias	Skeletal dysplasia	[102]
Panel with genes involved in pituitary ontogenesis and in GH secretion	Combined pituitary hormone deficiency	[103]
Genomic approach		
Array-based CNV analyses (SNPa or aCGH)	Syndromic children, especially those with developmental delay, intellectual disability	[75]
Whole exome sequencing	Short stature of undetermined cause with high probability of being a monogenic condition	[34]

CNV: Copy-number variation; MLPA: Multiplex ligation-dependent probe amplification; SNAa: single nucleotide polymorphism arrays; aCGH: comparative genomic hybridization.

that explains their growth deficit [88]. A proportion of these children are at the mild end of the phenotypic spectrum of a known syndromic disorder associated with short stature [79,80], such as Noonan syndrome or DiGeorge syndrome. Additionally, several studies have associated specific genes with the isolated short stature phenotype, including heterozygous pathogenic variants in *GHR* [89] and *SHOX* [90] in children classified as ISS, and other studies have broadened the genes involved (Table 6). The most consistent and frequent findings in children originally classified as ISS are heterozygous variants in genes involved in growth plate development: *SHOX* [24], *ACAN* [40], *NPR2* [23,91], *NPPC* [92] and *IHH* [25]. Each of these genes accounts for a low proportion of cases of short stature (1–2% or less) but the percentage may be significantly higher in familial short stature [91]. Defects in these genes cause a variable degree of short stature with non-specific phenotypes and are usually inherited in an autosomal dominant manner. This lack of specific characteristics makes it difficult to recognize without a molecular genetic study. For this reason, it is not effective to apply a candidate gene analysis, so a multiple-gene testing approach using next-generation sequencing (NGS) or the use of WES is preferable. The choice between the two will depend on the availability and cost-benefit evaluation. However the approach with WES has been presented as more advantageous [93]. Even when using the WES approach, the analysis of these patients should prioritize the genes already associated with the isolated short stature phenotype and genes associated with syndromic conditions with great phenotypic variability that are already documented (Tables 5 and 6).

At present, most patients will not have a conclusive result after genetic analysis. It will be important to learn if there is a relationship between a given genetic diagnosis and the response to rhGH treatment [24,40,94] or long-term health consequences [40]. It is likely that with the increased availability of genetic studies, the primary way to investigate short stature patients will change. In the near future, genetic testing may become the standard method of investigation of children with isolated short stature [88].

5. Initial rhGH-management and monitoring of rhGH therapy

5.1. GH dose adjustment and monitoring

The main goal of rhGH therapy in children is to increase and normalize growth velocity and to achieve an adequate adult height. The most common method of adjusting rhGH dose in order to obtain and maintain the expected growth velocity is based on body weight and growth velocity, although body surface area is also used [51]. Prediction models are available to calculate the initial dose based on diagnosis and goal as well as to follow the adequacy of dose/response [113].

Table 6
Genes associated with isolated short stature phenotype.

Gene	First report	Inheritance Pattern	Frequency[a]	Evidence of association[b]	Observation	Ref
GHR	1995	AD	NA	Limited	Mild GH insensitivity phenotype (Low IGF-1 and GHBP levels	[89]
SHOX	1997	AD	1 to 16%	Definitive	Mild body disproportion	[90]
GH1	2003	AD	NA	Limited		[104]
IGF1R	2003	AD	NA	Moderate	Majority born SGA and elevated IGF-1 levels	[105]
IGFALS	2004	AR	NA	Moderate	severe IGF-1 and IGFBP-3 deficiency disproportionate with mild height deficit	[106]
GHSR	2006	AD/AR	NA	Limited	It may be associated with GHD in the same family	[107]
IGF1	2013	AD	NA	Limited		[108]
ACAN	2014	AD	1.4 to 2.1%	Strong	Advance bone age	[20]
NPR2	2014	AD	1.2 to 3.4%	Strong		[109]
FGFR3	2015	AD	NA	Limited		[110]
PAPPA2	2016	AR	NA	Limited	Elevated IGF-1 and IGFBP-3 levels	[50]
IHH	2018	AD	1.6%	Moderate	Shortening of middle phalange of 2nd and 5th finguer	[25]
NPPC	2018	AD	NA	Limited	Mild brachydactyly	[91]
STAT5B	2018	AD	NA	Limited	Mild GH insensitivity phenotype with eczema	[111]

NA – not available; AD – Autosomal dominant; AR – Autosomal recessive.
[a] frequency observed in studies that evaluated unselected children with isolated short stature (ISS or non-syndromic SGA).
[b] Strength of evidence that changes in this gene are associated with the isolated short stature phenotype [112].

Published charts for the expected growth velocity during the first year of treatment may help assess whether the initial response is appropriate [114]. An insufficient response may indicate the presence of associated conditions preventing the expected growth response or inadequate compliance to treatment, but may also suggest that the initial diagnosis is not correct; it may even suggest that there is a reason to re-evaluate the benefits of the treatment.

The initial studies that led to the approval of rhGH used growth velocity and change in weight to adjust rhGH dosage. In 2007, Cohen *et al* demonstrated that IGF-I levels could be used to adjust rhGH dosage in children with GHD and ISS. They demonstrated that maintaining the IGF-1 level close to the mean for age and gender elicited a similar 2 year growth response compared with methods of rhGH dosage based on weight, but using a lower mean dose of rhGH [115,116] and avoiding supraphysiological serum levels of IGF—I, suggesting that this strategy could improve safety as population studies demonstrated a correlation between higher IGF-I and some cancers in the normal adult population [117]. On the other hand, in conditions associated with mild GH and/or IGF-I resistance, higher rhGH doses and/or IGF-I serum levels to achieve the expected clinical response [118,119,120] may be necessary. There are no data demonstrating that above normal levels of IGF-I during rhGH therapy causes any harm [118].

There are two other aspects to consider when treating children with rhGH: (1) different individuals may have different sensitivity to GH and to IGF-I and the sensitivity in different tissues in the same individual may also differ, with higher doses of GH and levels of IGF-I causing different local effects in each person and (2) IGF-I circulates in serum bound to IGFBPs and ALS. Some population studies demonstrated that higher serum IGFBP-3 is associated with a lower incidence of malignancies [121]. It has been suggested that free IGF-I index or IGF-I/IGFBP-3 be used as a safety measure, although there are no data to support such practice.

In clinical practice, GHD children need replacement of "physiological" rhGH and ideal therapy would maintain IGF-I within the appropriate levels for gender and age. Therefore, measurement of IGF-I concentrations may be used with the goal of normalizing serum IGF—I, as suggested by Cohen et al. [122]. On the other hand, some non-GHD children may require supraphysiologic levels of IGF-I to obtain the desired beneficial aspects of treatment. Since there are inadequate data available to indicate a safe upper limit for serum IGF-I concentrations and the safety implications of higher serum IGF-I levels are unknown, if an adequate growth velocity is obtained with normal levels of IGF-I in these children, supraphysiological levels may not need to be maintained.

5.2. Care with unmasking other conditions

5.2.1. Cortisol deficiency

GH inhibits 11β-hydroxysteroid dehydrogenase type 1, which is responsible for the conversion of cortisone (inactive) into cortisol (active). Initiation of rhGH therapy in patients with subclinical adrenocorticotropic hormone (ACTH) deficiency may induce symptomatic adrenal insufficiency requiring glucocorticoid replacement. Patients already on cortisol replacement may need an upward dose adjustment. Caretakers should look for symptoms of adrenal insufficiency after starting GH in patients at risk for ACTH deficiency [118].

5.2.2. Hypothyroidism

GH increases the peripheral conversion of thyroxine (T4) to tri-iodothyronine. Commencing GH replacement may therefore unmask preexisting central hypothyroidism as defined by a fall of serum-free T4 into the subnormal range. Thyroid function should be monitored and adjustment of the T4 dose may be needed after initiation of rhGH [118].

5.2.3. Diabetes Mellitus

GH increases insulin resistance but it is not associated with the development of diabetes mellitus, although the addition of rhGH in children with impaired insulin secretion/action, may cause enough insulin resistance leading to the appearance of hyperglycemia. Hemoglobin A1C and glucose should be monitored in patients at risk for developing diabetes mellitus [118].

5.3. Possible complications during rhGH therapy

Daily rhGH therapy has a well-established record of safety and efficacy for the treatment of adults with GHD and children with multiple causes of growth failure. > 500,000 patient years of safety data have been collected in clinical trials and post-marketing surveillance registries while children and adults received treatment. During treatment, rhGH therapy has been shown to be associated with rare complications, including intracranial hypertension and slipped capital femoral epiphysis [118]. In children with PWS and obese adults with GHD, obstructive sleep apnea is a concern. Pancreatitis [118] and prepubertal gynecomastia [123] have been reported in children receiving rhGH. More common treatment-related side effects of daily rhGH therapy include worsening of existent scoliosis, myalgias, arthralgias and edema. A comprehensive review of the safety aspects of GH therapy, both in children and adults, has recently been published [118].

5.4. Long term safety

There are fewer data available to assess the long-term safety of daily rhGH therapy. The Childhood Cancer Survivor Study has provided important information about the risk of primary tumor recurrence and development of secondary malignancies in children receiving rhGH after treatment for cancer. The SAGhE study investigated the safety of daily rhGH in young adults who received treatment as children [124].

5.4.1. Cancer survival children and adolescents

In 2002 Sklar et al. reported that children treated for cancers who received rhGH had a 3.21-fold (1.88–5.46) high chance of developing a second tumor [125]. The same group subsequent demonstrated in 2006 that after 32 more months of follow-up, the risk remained elevated although it decreased to 2.15-fold (1.33–3.47), mainly due to the higher incidence of second malignancies in patients who had not received rhGH [126]. These data indicated that although cancer survivors treated with GH appear to have an increased risk of developing second neoplasms compared with survivors who were not treated, the elevation of risk due to GH use appears to diminish with increasing length of follow-up. Other studies did not demonstrate this increased risk [127] including a recent systematic review and meta-analysis [128]. The Growth Hormone Research Society position is that the association between GH therapy and the risk of second tumors is insufficient to preclude use of rhGH for licensed indications in children [118]. In children with a history of brain radiation, the risk of non-malignant meningioma was increased, but there appeared to be no additional risk of meningioma in those children who had received both radiation and rhGH therapy. In various studies, there was some evidence of increased risk of other secondary malignancies including sarcoma. The safety of rhGH in conditions with a predisposition to developing cancer, including Bloom Syndrome, Fanconi Anemia, Neurofibromatosis type 1 and Down Syndrome remain controversial.

5.4.2. Patients without previous history of malignancy

The only long-term study to investigate the safety of rhGH is the SAGhE study [124]. Initial partial reports raised the possibility of increased mortality of patients with idiopathic short stature, isolated GHD or SGA who received rhGH [129]. The results of a more complete evaluation showed that there was no clear increased risk in patients with growth failure without other major disease [130]. In the French SAGhE cohort, an increased risk of death due to cerebrovascular disease, including hemorrhagic stroke, was seen [129]. However, this risk

was not seen in the SAGhE cohort from Belgium, Netherlands and Sweden [131]. In addition, adjustment of mortality risk for low birth weight was found to reduce the risk of mortality [132]. The incidence of bone and bladder cancers were significantly raised in rhGH-treated patients without previous cancer, but the absolute numbers of tumors was small. Cancer risk was unrelated to duration or cumulative dose of rhGH treatment [130]. These studies emphasize the different health risks in individuals with short stature compared to those of normal stature, the need to compare outcomes to appropriate control groups and the need to develop mechanisms to allow continued collection of long-term safety data.

5.5. Management of the poorly growing child on growth hormone

Treatment with rhGH at the currently used doses increases adult height in most children with short stature. There are two main groups of children who grow poorly on rhGH: those who did not increase height velocity when starting treatment and those who had an increment in the growth velocity but subsequently changed to a sub-normal height velocity [133,134].

The expected initial response of rhGH treatment is an increase in height SDS and height velocity resulting in a later increment in adult height. Because there is a continuum of GH responses, the definition of nonresponsiveness is arbitrary. Suggested criteria for poor first year response include height velocity SDS less than −1 or change in height SDS < 0.3–0.5, depending on age. There are also first year growth response charts for different conditions as well as prediction models. Those can be used to assess adequacy of initial height velocity [20].

5.5.1. Children who did not increase HV upon starting treatment with rhGH

The main reasons for a child not to have an increment in growth velocity when starting rhGH are: (1) lack of adequate storage of the rhGH, (2) lack of understanding of the methods of administration of medication or non-compliance, (3) inaccurate diagnosis, and (4) unrealistically high growth expectations. If the initial response is considered inadequate, the approach is to review with patient and family the understanding of treatment and techniques of administration of the medication. If those are appropriate, changes in serum IGF-I when comparing pre and post treatment may help. If pretreatment serum IGF-I levels were higher than expected, the initial diagnosis should be questioned. If there was no change in IGF−I, GH insensitivity, conditions that affect growth and IGF-I synthesis (inflammatory bowel disease for example) and adherence issues should be further investigated.

5.5.2. Children with a normal initial response but subsequent decreased height velocity

The main reasons for a decrement in growth velocity while on rhGH are: (1) lack of adequate compliance/adherence, (2) development of antibodies to GH, (3) development of a secondary condition that affects growth (hypothyroidism, enteropathies – inflammatory bowel disease or celiac disease, Cushing's disease, other chronic illnesses/malnutrition), (4) lack of sex steroid exposure at the appropriate ages, and (5) closure of growth plate.

When there was an initial response followed by a low height velocity, lack of compliance is the most common cause. In patients with isolated GHD, the development of anti-GH antibodies should be investigated in those with type 1a GHD. Investigating other secondary causes for failure to grow can initially be oriented based on risks specifics for each group. For example, girls with Turner syndrome have a higher chance of developing primary hypothyroidism. Patients with abnormal pituitary anatomy or post cranial radiation may develop central hypothyroidism. In children with peripubertal age, the lack of sex steroids may affect height velocity. Another aspect to remember is that complete closure of the bone epiphyses arrests growth.

5.6. The transition from childhood to adult GH therapy

The transition phase is defined herein as a broad set of physical and psychosocial changes going from late puberty and ending with full adult maturation [135]. GHD patients may require the continuation of rhGH treatment in order to attain full skeletal mineralization and alleviate the potential changes in body composition and lipid metabolism associated with cardiovascular disease found in GHD adults. Many patients with childhood onset GHD do not have GH deficiency when retested after stopping rhGH therapy as adolescents. Thus, it is important to identify those who have a higher probability of maintaining the GHD status in adult life. Several guidelines for the transition phase have been published elsewhere [59,135,136,137].

6. Emerging diagnostic tools and therapies for short stature

6.1. Diagnosis

Although there has been significant progress in the treatment of children with growth failure, the diagnostic categorization of these children remains a challenge. Application of genomic, proteomic and metabolomic testing may improve our ability to categorize poorly growing children and predict which one will respond well to treatment. New agents for growth hormone stimulation tests, such as Macimorelin, an oral ghrelin receptor agonist, may improve the diagnostic accuracy of provocative tests in children, adolescents during the transition period and in adults. Macimorelin was approved in 2017 by the FDA for the diagnosis of GHD during adult life with accuracy comparable with that of the insulin tolerance test and it was shown to be safe and convenient [138]. No studies in children are yet available.

6.2. Treatment of achondroplasia with future perspective in ISS

Fibroblast growth factor receptor 3 (*FGFR3*) is an important regulator of bone formation. Gain-of-function mutations in the *FGFR3* gene result in chondrodysplasias which include achondroplasia (ACH) and hypochondroplasia. The skeletal phenotype of patients with ACH results from defective proliferation and differentiation of the chondrocytes in the growth plate. BMN111, a C-type natriuretic peptide (CNP) analog (BMN111) acts as a key regulator of longitudinal bone growth by downregulating the mitogen-activated protein kinase pathway, which is activated as a result of a FGFR3 gain-of-function mutation. In 2014, a clinical trial (phase 2, https://clinicaltrials.gov/ct2/show/NCT02724228) of BMN111 (Vosoritide) in pediatric patients with ACH started [139] and a phase 3 trial is currently underway (https://clinicaltrials.gov/ct2/show/NCT03197766).

6.3. Long acting growth hormone

Extensive reviews of the emerging field of long-acting growth hormone (LAGH) have recently been published [140,141]. As the era of LAGH approaches, we need to consider whether there will be additional safety risks of LAGH compared to daily rhGH. In this regard, we need to consider issues related to the persistent elevation of GH and GH-related biomarkers, such as IGF−I, as well as issues related to the mechanisms of making GH long-acting. Depending upon the structure of LAGH, there may be off target effects due to components of the LAGH not present in rhGH.

Treatment with daily rhGH given at bedtime attempts to mimic the normal daily profile of increased GH production overnight. However, daily rhGH is a single peak of GH action which differs from physiologic GH production of multiple GH pulses of different duration and intensity. Thus, our current daily rhGH treatment regimen does not provide a physiologic GH profile. LAGH products will likely have differing pharmacokinetic profiles of GH release from the injection site into the blood stream, to the target tissue and to the GH receptor.

The peak and trough levels of IGF-I during daily rhGH and LAGH therapy have been an area of intense debate. The goal of GH therapy has been increasing the IGF-I to promote growth. It remains to be determined if LAGH will achieve similar or better growth than daily rhGH and whether individualizing LAGH therapy to target an IGF-I in the upper part of the normal range would improve efficacy without decreasing safety. Due to the differing pharmacodynamics profile of different forms of LAGH, it will be important to determine the best time to measure IGF-I for safety and efficacy.

References

[1] WHO Multicentre Growth Reference Study Group, WHO Child Growth Standards based on length/height, weight and age, Acta Paediatr. Suppl. 450 (2006 Apr) 76–85.

[2] A.D. Rogol, G.F. Hayden, Etiologies and early diagnosis of short stature and growth failure in children and adolescents, J. Pediatr. 164 (5 Suppl) (2014 May) S1–14.e6.

[3] A. Habel, M.J. McGinn 2nd, E.H. Zackai, N. Unanue, D.M. McDonald-McGinn, Syndrome-specific growth charts for 22q11.2 deletion syndrome in Caucasian children, Am. J. Med. Genet. A 158A (11) (2012 Nov) 2665–2671.

[4] A.C. Malaquias, A.S. Brasil, A.C. Pereira, I.J. Arnhold, B.B. Mendonca, D.R. Bertola, A.A. Jorge, Growth standards of patients with Noonan and Noonan-like syndromes with mutations in the RAS/MAPK pathway, Am. J. Med. Genet. A 158A (11) (2012 Nov) 2700–2706.

[5] L. Tofts, S. Das, F. Collins, K.L.O. Burton, Growth charts for Australian children with achondroplasia, Am. J. Med. Genet. A 173 (8) (2017 Aug) 2189–2200.

[6] B.S. Zemel, M. Pipan, V.A. Stallings, W. Hall, K. Schadt, D.S. Freedman, P. Thorpe, Growth charts for children with down syndrome in the United States, Pediatrics 136 (5) (2015 Nov) e1204–e1211.

[7] P. Scherdel, R. Reynaud, C. Pietrement, J.F. Salaün, M. Bellaïche, M. Arnould, B. Chevallier, H. Piloquet, E. Jobez, J. Cheymol, E. Bichara, EBGM III study group, B. Heude, M. Chalumeau, Priority target conditions for algorithms for monitoring children's growth: interdisciplinary consensus, PLoS One 12 (4) (2017 Apr 27) e0176464.

[8] D. Fayter, J. Nixon, S. Hartley, A. Rithalia, G. Butler, M. Rudolf, P. Glasziou, M. Bland, L. Stirk, M. Westwood, Effectiveness and cost-effectiveness of height-screening programmes during the primary school years: a systematic review, Arch. Dis. Child. 93 (4) (2008) 278–284.

[9] D.A. Silva, A. Pelegrini, E.L. Petroski, A.C. Gaya, Comparison between the growth of Brazilian children and adolescents and the reference growth charts: data from a Brazilian project, J. Pediatr. 86 (2) (2010) 115–120.

[10] P. Scherdel, J. Botton, M.F. Rolland-Cachera, J. Léger, F. Pelé, P.Y. Ancel, C. Simon, K. Castetbon, B. Salanave, H. Thibault, S. Lioret, S. Péneau, G. Gusto, M.A. Charles, B. Heude, Should the WHO growth charts be used in France? PLoS One 10 (3) (2015) e0120806.

[11] M. de Onis, A.W. Onyango, E. Borghi, C. Garza, H. Yang, WHO Multicentre Growth Reference Study Group. Comparison of the World Health Organization (WHO) Child Growth Standards and the National Center for Health Statistics/WHO international growth reference: implications for child health programmes, Public Health Nutr. 9 (7) (2006) 942–947.

[12] M. Bonthuis, K.J. van Stralen, E. Verrina, A. Edefonti, E.A. Molchanova, A.C. Hokken-Koelega, F. Schaefer, K.J. Jager, Use of national and international growth charts for studying height in European children: development of up-to-date European height-for-age charts, PLoS One 7 (8) (2012) e42506.

[13] S. Banerjee, R.J. Morgan, S.A. Rees, A.H. Latif, Height screening at school: ineffective without high standards and adequate resources, Arch. Dis. Child. 88 (6) (2003) 477–481 (discussion 477-81).

[14] J.M. Wit, P.E. Clayton, A.D. Rogol, M.O. Savage, P.H. Saenger, P. Cohen, Idiopathic short stature: definition, epidemiology, and diagnostic evaluation, Growth Hormon. IGF Res. 18 (2) (2008 Apr) 89–110.

[15] J.M. Tanner, H. Goldstein, R.H. Whitehouse, Standards for children's height at ages 2-9 years allowing for heights of parents, Arch. Dis. Child. 45 (244) (1970 Dec) 755–762.

[16] C.M. Wright, T.D. Cheetham, The strengths and limitations of parental heights as a predictor of attained height, Arch. Dis. Child. 81 (3) (1999 Sep) 257–260.

[17] F.K. Grote, P. van Dommelen, W. Oostdijk, S.M. de Muinck Keizer-Schrama, P.H. Verkerk, J.M. Wit, S. van Buuren, Developing evidence-based guidelines for referral for short stature, Arch. Dis. Child. 93 (3) (2008) 212–217.

[18] S.E. Stalman, I. Hellinga, P. van Dommelen, R.C. Hennekam, A. Saari, U. Sankilampi, L. Dunkel, J.M. Wit, G.A. Kamp, F.B. Plötz, Application of the Dutch, Finnish and British screening guidelines in a Cohort of children with growth failure, Horm. Res. Paediatr. 84 (6) (2015) 376–382.

[19] S. van Buuren, P. van Dommelen, G.R. Zandwijken, F.K. Grote, J.M. Wit, P.H. Verkerk, Towards evidence based referral criteria for growth monitoring, Arch. Dis. Child. 89 (4) (2004) 336–341.

[20] P. Cohen, A.D. Rogol, C.L. Deal, P. Saenger, E.O. Reiter, J.L. Ross, S.D. Chernausek, M.O. Savage, J.M. Wit, ISS Consensus Workshop participants. 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. 93 (11) (2007) 4210–4217.

[21] J.M. Wit, W. Oostdijk, M. Losekoot, H.A. van Duyvenvoorde, C.A. Ruivenkamp, S.G. Kant, MECHANISMS IN ENDOCRINOLOGY: novel genetic causes of short stature, Eur. J. Endocrinol. 174 (4) (2016) R145–R173.

[22] O. Nilsson, M.H. Guo, N. Dunbar, J. Popovic, D. Flynn, C. Jacobsen, J.C. Lui, J.N. Hirschhorn, J. Baron, A. Dauber, Short stature, accelerated bone maturation, and early growth cessation due to heterozygous aggrecan mutations, J. Clin. Endocrinol. Metab. 99 (8) (2014) E1510–E1518.

[23] G.A. Vasques, I.J. Arnhold, A.A. Jorge, Role of the natriuretic peptide system in normal growth and growth disorders, Horm. Res. Paediatr. 82 (4) (2014) 222–229.

[24] A.C. Malaquias, R.C. Scalco, E.G. Fontenele, E.F. Costalonga, A.D. Baldin, A.F. Braz, M.F. Funari, M.Y. Nishi, G. Guerra-Junior, B.B. Mendonca, I.J. Arnhold, A.A. Jorge, 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. 80 (6) (2013) 449–456.

[25] G.A. Vasques, M.F.A. Funari, F.M. Ferreira, M. Aza-Carmona, L. Sentchordi-Montané, J. Barraza-García, A.M. Lerario, G.L. Yamamoto, M.S. Naslavsky, Y.A.O. Duarte, D.R. Bertola, K.E. Heath, A.A.L. Jorge, IHH gene mutations causing short stature with nonspecific skeletal abnormalities and response to growth hormone therapy, J. Clin. Endocrinol. Metab. 103 (2) (2018) 604–614.

[26] J. Baron, L. Sävendahl, F. De Luca, A. Dauber, M. Phillip, J.M. Wit, O. Nilsson, Short and tall stature: a new paradigm emerges, Nat. Rev. Endocrinol. 11 (12) (2015 Dec) 735–746.

[27] Y.H. Jee, A.C. Andrade, J. Baron, O. Nilsson, Genetics of short stature, Endocrinol. Metab. Clin. N. Am. 46 (2) (2017) 259–281.

[28] R. Lindsay, M. Feldkamp, D. Harris, J. Robertson, M. Rallison, Utah Growth Study: growth standards and the prevalence of growth hormone deficiency, J. Pediatr. 125 (1) (1994) 29–35.

[29] S. Sisley, M.V. Trujillo, J. Khoury, P. Backeljauw, Low incidence of pathology detection and high cost of screening in the evaluation of asymptomatic short children, J. Pediatr. 163 (4) (2013) 1045–1051.

[30] W. Oostdijk, F.K. Grote, S.M. de Muinck Keizer-Schrama, J.M. Wit, Diagnostic approach in children with short stature, Horm. Res. 72 (4) (2009) 206–217.

[31] A.M. Fredriks, S. van Buuren, W.J. van Heel, R.H. Dijkman-Neerincx, S.P. Verloove-Vanhorick, J.M. Wit, Nationwide age references for sitting height, leg length, and sitting height/height ratio, and their diagnostic value for disproportionate growth disorders, Arch. Dis. Child. 90 (8) (2005) 807–812.

[32] S.G. Kant, F. Grote, M.H. de Ru, W. Oostdijk, H.M. Zonderland, M.H. Breuning, J.M. Wit, Radiographic evaluation of children with growth disorders, Horm. Res. 68 (6) (2007) 310–315.

[33] T.K. Homma, A.C.V. Krepischi, T.K. Furuya, R.S. Honjo, A.C. Malaquias, D.R. Bertola, S.S. Costa, A.P. Canton, R.A. Roela, B.L. Freire, C.A. Kim, C. Rosenberg, A.A.L. Jorge, Recurrent copy number variants associated with syndromic short stature of unknown cause, Horm. Res. Paediatr. 89 (1) (2018) 13–21.

[34] A. Dauber, R.G. Rosenfeld, J.N. Hirschhorn, Genetic evaluation of short stature, J. Clin. Endocrinol. Metab. 99 (9) (2014) 3080–3092.

[35] T.Y. Tan, O.J. Dillon, Z. Stark, D. Schofield, K. Alam, R. Shrestha, B. Chong, D. Phelan, G.R. Brett, E. Creed, A. Jarmolowicz, P. Yap, M. Walsh, L. Downie, D.J. Amor, R. Savarirayan, G. McGillivray, A. Yeung, H. Peters, S.J. Robertson, A.J. Robinson, I. Macciocca, S. Sadedin, K. Bell, A. Oshlack, P. Georgeson, N. Thorne, C. Gaff, S.M. White, Diagnostic impact and cost-effectiveness of whole-exome sequencing for ambulant children with suspected monogenic conditions, JAMA Pediatr. 171 (9) (2017) 855–862.

[36] W.W. Greulich, S.Y. Pyle (Eds.), Radiographic Atlas of Skeletal Development of the Hand and Wrist, 2nd ed, Stanford University Press, Stanford, CA, 1959xvi. (256 p).

[37] J.M. Tanner, et al., Assessment of Skeletal Maturity and Prediction of Adult Height (TW3 Method), 3rd ed, Saunders Ltd, 2001.

[38] N. Bayley, S.R. Pinneau, Tables for predicting adult height from skeletal age: revised for use with the Greulich-Pyle hand standards, J. Pediatr. 40 (4) (1952) 423–441.

[39] H.H. Thodberg, Clinical review: an automated method for determination of bone age, J. Clin. Endocrinol. Metab. 94 (7) (2009) 2239–2244.

[40] A. Gkourogianni, M. Andrew, L. Tyzinski, M. Crocker, J. Douglas, N. Dunbar, J. Fairchild, M.F. Funari, K.E. Heath, A.A. Jorge, T. Kurtzman, S. LaFranchi, S. Lalani, J. Lebl, Y. Lin, E. Los, D. Newbern, C. Nowak, M. Olson, J. Popovic, Š. Pruhová, L. Elblova, J.B. Quintos, E. Segerlund, L. Sentchordi, M. Shinawi, E.L. Stattin, J. Swartz, A.G. Angel, S.D. Cuéllar, H. Hosono, P.A. Sanchez-Lara, V. Hwa, J. Baron, O. Nilsson, A. Dauber, Clinical characterization of patients with autosomal dominant short stature due to Aggrecan mutations, J. Clin. Endocrinol. Metab. 102 (2) (2017) 460–469.

[41] F.K. Grote, W. Oostdijk, S.M. de Muinck Keizer-Schrama, F.W. Dekker, P.H. Verkerk, J.M. Wit, Growth monitoring and diagnostic work-up of short stature: an international inventorization, J. Pediatr. Endocrinol. Metab. 18 (11) (2005) 1031–1038.

[42] P.C. Sizonenko, P.E. Clayton, P. Cohen, R.L. Hintz, T. Tanaka, Z. Laron, Diagnosis and management of growth hormone deficiency in childhood and adolescence. Part 1: diagnosis of growth hormone deficiency, Growth Hormon. IGF Res. 11 (3) (2001) 137–165.

[43] J.G. Sfeir, N.E. Kittah, S.U. Tamhane, S. Jasim, W. Chemaitilly, L. Cohen, M.H. Murad, Diagnosis of growth hormone deficiency as a late effect of radiotherapy in survivors of childhood cancers, J. Clin. Endocrinol. Metab. (2018 Jun 29), https://doi.org/10.1210/jc.2018-01204 (Epub ahead of print).

[44] C.H. Gravholt, N.H. Andersen, G.S. Conway, O.M. Dekkers, M.E. Geffner, K.O. Klein, A.E. Lin, N. Mauras, C.A. Quigley, K. Rubin, D.E. Sandberg, T.C.J. Sas, M. Silberbach, V. Söderström-Anttila, K. Stochholm, J.A. van Alfen-van derVelden, J. Woelfle, P.F. Backeljauw, International Turner Syndrome Consensus Group,

Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome meeting, Eur. J. Endocrinol. 177 (3) (2017) G1–G70.
[45] M.J. Walenkamp, J.M. Wit, Genetic disorders in the GH IGF-I axis in mouse and man, Eur. J. Endocrinol. 157 (Suppl. 1) (2007) S15–S26.
[46] J. Klammt, W. Kiess, R. Pfäffle, IGF1R mutations as cause of SGA, Best Pract. Res. Clin. Endocrinol. Metab. 25 (1) (2011) 191–206.
[47] M.O. Savage, C.P. Burren, R.G. Rosenfeld, The continuum of growth hormone-IGF-I axis defects causing short stature: diagnostic and therapeutic challenges, Clin. Endocrinol. (Oxf) 72 (6) (2010 Jun) 721–728.
[48] W.F. Blum, A. Alherbish, A. Alsagheir, A. El Awwa, W. Kaplan, E. Koledova, M.O. Savage, The growth hormone-insulin-like growth factor-I axis in the diagnosis and treatment of growth disorders, Endocr. Connect. 7 (6) (2018 Jun) R212–R222.
[49] Y. Shen, J. Zhang, Y. Zhao, Y. Yan, Y. Liu, J. Cai, Diagnostic value of serum IGF-1 and IGFBP-3 in growth hormone deficiency: a systematic review with meta-analysis, Eur. J. Pediatr. 174 (4) (2015) 419–427.
[50] A. Dauber, M.T. Muñoz-Calvo, V. Barrios, H.M. Domené, S. Kloverpris, C. Serra-Juhé, V. Desikan, J. Pozo, R. Muzumdar, G.Á. Martos-Moreno, F. Hawkins, H.G. Jasper, C.A. Conover, J. Frystyk, S. Yakar, V. Hwa, J.A. Chowen, C. Oxvig, R.G. Rosenfeld, L.A. Pérez-Jurado, J. Argente, Mutations in pregnancy-associated plasma protein A2 cause short stature due to low IGF-I availability, EMBO Mol. Med. 8 (4) (2016) 363–374.
[51] Growth Hormone Research Society, Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. GH Research Society, J. Clin. Endocrinol. Metab. 85 (11) (2000 Nov) 3990–3993.
[52] G. Binder, M. Weidenkeller, G. Blumenstock, M. Langkamp, K. Weber, A.R. Franz, Rational approach to the diagnosis of severe growth hormone deficiency in the newborn, J. Clin. Endocrinol. Metab. 95 (5) (2010 May) 2219–2226.
[53] R.G. Rosenfeld, K. Albertsson-Wikland, F. Cassorla, S.D. Frasier, Y. Hasegawa, R.L. Hintz, S. Lafranchi, B. Lippe, L. Loriaux, S. Melmed, et al., Diagnostic controversy: the diagnosis of childhood growth hormone deficiency revisited, J. Clin. Endocrinol. Metab. 80 (5) (1995 May) 1532–1540.
[54] E.A. Chaler, Ballerini Ga, J.M. Lazzati, M. Maceiras, M. Frusti, I. Bergada, M.A. Rivarola, A. Belgorosky, G. Ropelato, Cut-off values of serum growth hormone (GH) in pharmacological stimulation tests (PhT) evaluated in short-statured children using a chemiluminescent immunometric assay (ICMA) calibrated with the International Recombinant Human GH Standard 98/574, Clin. Chem. Lab. Med. 51 (5) (2013 May) e95–e97.
[55] A. Secco, N. di Iorgi, F. Napoli, E. Calandra, M. Ghezzi, C. Frassinetti, S. Parodi, M.R. Casini, R. Lorini, S. Loche, M. Maghnie, The glucagon test in the diagnosis of growth hormone deficiency in children with short stature younger than 6 years, J. Clin. Endocrinol. Metab. 94 (11) (2009 Nov) 4251–4257.
[56] T. Tanaka, P. Cohen, P.E. Clayton, Z. Laron, R.L. Hintz, P.C. Sizonenko, Diagnosis and management of growth hormone deficiency in childhood and adolescence–part 2: growth hormone treatment in growth hormone deficient children, Growth Hormon. IGF Res. 12 (5) (2002 Oct) 323–341.
[57] M.B. Ranke, J.M. Wit, Growth hormone – past, present and future, Nat. Rev. Endocrinol. 14 (5) (2018 May) 285–300.
[58] M. Lodefalk, O. Nilsson, To prime or not to prime – is that still a question? A comment on the US guidelines on growth hormone and insulin-like growth factor-i treatment in children and adolescents, Horm. Res. Paediatr. 88 (2) (2017) 179–180.
[59] A. Grimberg, S.A. DiVall, C. Polychronakos, D.B. Allen, L.E. Cohen, J.B. Quintos, W.C. Rossi, C. Feudtner, M.H. Murad, Guidelines for growth hormone and insulin-like growth factor-i treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-i deficiency, Horm. Res. Paediatr. 86 (6) (2016) 361–397.
[60] L. Lazar, M. Phillip, Is sex hormone priming in peripubertal children prior to growth hormone stimulation tests still appropriate? Horm. Res. Paediatr. 73 (4) (2010) 299–302.
[61] A. Albrecht, T. Penger, M. Marx, K. Hirsch, H.G. Dörr, Short-term adverse effects of testosterone used for priming in prepubertal boys before growth hormone stimulation test, J. Pediatr. Endocrinol. Metab. 31 (1) (2018 Jan 26) 21–24.
[62] J.G. Sfeir, N.E. Kittah, S.U. Tamhane, S. Jasim, W. Chemaitilly, L. Cohen, M.H. Murad, Diagnosis of growth hormone deficiency as a late effect of radiotherapy in survivors of childhood cancers, J. Clin. Endocrinol. Metab. (2018 Jun 29), https://doi.org/10.1210/jc.2018-01204 (Epub ahead of print).
[63] L. Bonafe, V. Cormier-Daire, C. Hall, R. Lachman, G. Mortier, S. Mundlos, G. Nishimura, L. Sangiorgi, R. Savarirayan, D. Sillence, J. Spranger, A. Superti-Furga, M. Warman, S. Unger, Nosology and classification of genetic skeletal disorders: 2015 revision, Am. J. Med. Genet. A 167A (12) (2015) 2869–2892.
[64] L.H. Seaver, M. Irons, American College of Medical Genetics (ACMG) Professional Practice and Guidelines Committee, ACMG practice guideline: genetic evaluation of short stature, Genet. Med. 11 (6) (2009) 465–470.
[65] J.M. Wit, W. Kiess, P. Mullis, Genetic evaluation of short stature, Best Pract. Res. Clin. Endocrinol. Metab. 25 (1) (2011) 1–17.
[66] A. Dauber, J. Stoler, E. Hechter, J. Safer, J.N. Hirschhorn, Whole exome sequencing reveals a novel mutation in CUL7 in a patient with an undiagnosed growth disorder, J. Pediatr. 162 (1) (2013) 202–204 (e1).
[67] C. de Bruin, C. Finlayson, M.F. Funari, G.A. Vasques, B. Lucheze Freire, A.M. Lerario, M. Andrew, V. Hwa, A. Dauber, A.A. Jorge, Two patients with severe short stature due to a FBN1 mutation (p.Ala1728Val) with a mild form of acromicric dysplasia, Horm. Res. Paediatr. 86 (5) (2016) 342–348.
[68] S.R. Wang, H. Carmichael, S.F. Andrew, T.C. Miller, J.E. Moon, M.A. Derr, V. Hwa, J.N. Hirschhorn, A. Dauber, Large-scale pooled next-generation sequencing of 1077 genes to identify genetic causes of short stature, J. Clin. Endocrinol. Metab. 98 (8) (2013) E1428–E1437.
[69] J.S. Renes, R.H. Willemsen, A. Wagner, M.J. Finken, A.C. Hokken-Koelega, Bloom syndrome in short children born small for gestational age: a challenging diagnosis, J. Clin. Endocrinol. Metab. 98 (10) (2013) 3932–3938.
[70] Z. Stark, T.Y. Tan, B. Chong, G.R. Brett, P. Yap, M. Walsh, A. Yeung, H. Peters, D. Mordaunt, S. Cowie, D.J. Amor, R. Savarirayan, G. McGillivray, L. Downie, P.G. Ekert, C. Theda, P.A. James, J. Yaplito-Lee, M.M. Ryan, R.J. Leventer, E. Creed, I. Macciocca, K.M. Bell, A. Oshlack, S. Sadedin, P. Georgeson, C. Anderson, N. Thorne, Melbourne Genomics Health Alliance, C. Gaff, S.M. White, A prospective evaluation of whole-exome sequencing as a first-tier molecular test in infants with suspected monogenic disorders, Genet. Med. 18 (11) (2016) 1090–1096.
[71] Y. Yang, D.M. Muzny, F. Xia, Z. Niu, R. Person, Y. Ding, P. Ward, A. Braxton, M. Wang, C. Buhay, N. Veeraraghavan, A. Hawes, T. Chiang, M. Leduc, J. Beuten, J. Zhang, W. He, J. Scull, A. Willis, M. Landsverk, W.J. Craigen, M.R. Bekheirnia, A. Stray-Pedersen, P. Liu, S. Wen, W. Alcaraz, H. Cui, M. Walkiewicz, J. Reid, M. Bainbridge, A. Patel, E. Boerwinkle, A.L. Beaudet, J.R. Lupski, S.E. Plon, R.A. Gibbs, C.M. Eng, Molecular findings among patients referred for clinical whole-exome sequencing, JAMA 312 (18) (2014) 1870–1879.
[72] D.T. Miller, M.P. Adam, S. Aradhya, L.G. Biesecker, A.R. Brothman, N.P. Carter, D.M. Church, J.A. Crolla, E.E. Eichler, C.J. Epstein, W.A. Faucett, L. Feuk, J.M. Friedman, A. Hamosh, L. Jackson, E.B. Kaminsky, K. Kok, I.D. Krantz, R.M. Kuhn, C. Lee, J.M. Ostell, C. Rosenberg, S.W. Scherer, N.B. Spinner, D.J. Stavropoulos, J.H. Tepperberg, E.C. Thorland, J.R. Vermeesch, D.J. Waggoner, M.S. Watson, C.L. Martin, D.H. Ledbetter, Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies, Am. J. Hum. Genet. 86 (5) (2010) 749–764.
[73] Z. Stark, D. Schofield, K. Alam, W. Wilson, N. Mupfeki, I. Macciocca, R. Shrestha, S.M. White, C. Gaff, Prospective comparison of the cost-effectiveness of clinical whole-exome sequencing with that of usual care overwhelmingly supports early use and reimbursement, Genet. Med. 19 (8) (2017) 867–874.
[74] L.E.L.M. Vissers, K.J.M. van Nimwegen, J.H. Schieving, E.J. Kamsteeg, T. Kleefstra, H.G. Yntema, R. Pfundt, G.J. van der Wilt, L. Krabbenborg, H.G. Brunner, S. van der Burg, J. Grutters, J.A. Veltman, M.A.A.P. Willemsen, A clinical utility study of exome sequencing versus conventional genetic testing in pediatric neurology, Genet. Med. 19 (9) (2017) 1055–1063.
[75] T.K. Homma, A.C.V. Krepischi, T.K. Furuya, R.S. Honjo, A.C. Malaquias, D.R. Bertola, S.S. Costa, A.P. Canton, R.A. Roela, B.L. Freire, C.A. Kim, C. Rosenberg, A.A.L. Jorge, Recurrent copy number variants associated with syndromic short stature of unknown cause, Horm. Res. Paediatr. 89 (1) (2018) 13–21.
[76] A. Marchini, T. Ogata, G.A. Rappold, A track record on SHOX: from basic research to complex models and therapy, Endocr. Rev. 37 (4) (2016) 417–448.
[77] W.F. Blum, J.L. Ross, A.G. Zimmermann, C.A. Quigley, C.J. Child, G. Kalifa, C. Deal, S.L. Drop, G. Rappold, G.B. Cutler Jr., GH treatment to final height produces similar height gains in patients with SHOX deficiency and Turner syndrome: results of a multicenter trial, J. Clin. Endocrinol. Metab. 98 (8) (2013) E1383–E1392.
[78] B.L. Freire, T.K. Homma, M.F.A. Funari, A.M. Lerario, A.M. Leal, E.D.R.P. Velloso, A.C. Malaquias, Jorge AAL, Homozygous loss of function BRCA1 variant causing a Fanconi-anemia-like phenotype, a clinical report and review of previous patients, Eur. J. Med. Genet. 61 (3) (2018) 130–133.
[79] M.H. Guo, Y. Shen, E.C. Walvoord, T.C. Miller, J.E. Moon, J.N. Hirschhorn, A. Dauber, Whole exome sequencing to identify genetic causes of short stature, Horm. Res. Paediatr. 82 (1) (2014) 44–52.
[80] N.N. Hauer, B. Popp, E. Schoeller, S. Schuhmann, K.E. Heath, A. Hisado-Oliva, P. Klinger, C. Kraus, U. Trautmann, M. Zenker, C. Zweier, A. Wiesener, R. Abou Jamra, E. Kunstmann, D. Wieczorek, S. Uebe, F. Ferrazzi, C. Büttner, A.B. Ekici, A. Rauch, H. Sticht, H.G. Dörr, A. Reis, C.T. Thiel, Clinical relevance of systematic phenotyping and exome sequencing in patients with short stature, Genet. Med. 20 (6) (2018) 630–638.
[81] L. Shapiro, S. Chatterjee, D.G. Ramadan, K.M. Davies, M.O. Savage, L.A. Metherell, H.L. Storr, Whole-exome sequencing gives additional benefits compared to candidate gene sequencing in the molecular diagnosis of children with growth hormone or IGF-1 insensitivity, Eur. J. Endocrinol. 177 (6) (2017) 485–501.
[82] C. Bizzarri, G. Bottaro, Endocrine implications of neurofibromatosis 1 in childhood, Horm. Res. Paediatr. 83 (4) (2015) 232–241.
[83] A.A. Romano, J.E. Allanson, J. Dahlgren, B.D. Gelb, B. Hall, M.E. Pierpont, A.E. Roberts, W. Robinson, C.M. Takemoto, J.A. Noonan, Noonan syndrome: clinical features, diagnosis, and management guidelines, Pediatrics 126 (4) (2010) 746–759.
[84] G.P. Forlenza, A. Calhoun, K.B. Beckman, T. Halvorsen, E. Hamdoun, H. Zierhut, K. Sarafoglou, L.E. Polgreen, B.S. Miller, B. Nathan, A. Petryk, Next generation sequencing in endocrine practice, Mol. Genet. Metab. 115 (2–3) (2015 Jun-Jul) 61–71.
[85] K. Silventoinen, S. Sammalisto, M. Perola, D.I. Boomsma, B.K. Cornes, C. Davis, L. Dunkel, M. De Lange, J.R. Harris, J.V. Hjelmborg, M. Luciano, N.G. Martin, J. Mortensen, L. Nisticò, N.L. Pedersen, A. Skytthe, T.D. Spector, M.A. Stazi, G. Willemsen, J. Kaprio, Heritability of adult body height: a comparative study of twin cohorts in eight countries, Twin Res. 6 (5) (2003) 399–408.
[86] C. Durand, G.A. Rappold, Height matters-from monogenic disorders to normal variation, Nat. Rev. Endocrinol. 9 (3) (2013) 171–177.
[87] E. Marouli, M. Graff, C. Medina-Gomez, K.S. Lo, A.R. Wood, T.R. Kjaer, R.S. Fine,

Y. Lu, C. Schurmann, H.M. Highland, S. Rüeger, G. Thorleifsson, A.E. Justice, D. Lamparter, K.E. Stirrups, V. Turcot, K.L. Young, T.W. Winkler, T. Esko, T. Karaderi, A.E. Locke, N.G. Masca, M.C. Ng, P. Mudgal, M.A. Rivas, S. Vedantam, A. Mahajan, X. Guo, G. Abecasis, K.K. Aben, L.S. Adair, D.S. Alam, E. Albrecht, K.H. Allin, M. Allison, P. Amouyel, E.V. Appel, D. Arveiler, F.W. Asselbergs, P.L. Auer, B. Balkau, B. Banas, L.E. Bang, M. Benn, S. Bergmann, L.F. Bielak, M. Blüher, H. Boeing, E. Boerwinkle, C.A. Böger, L.L. Bonnycastle, J. Bork-Jensen, M.L. Bots, E.P. Bottinger, D.W. Bowden, I. Brandslund, G. Breen, M.H. Brilliant, L. Broer, A.A. Burt, A.S. Butterworth, D.J. Carey, M.J. Caulfield, J.C. Chambers, D.I. Chasman, Y.I. Chen, R. Chowdhury, C. Christensen, A.Y. Chu, M. Cocca, F.S. Collins, J.P. Cook, J. Corley, J.C. Galbany, A.J. Cox, G. Cuellar-Partida, J. Danesh, G. Davies, P.I. de Bakker, G.J. de Borst, S. de Denus, M.C. de Groot, R. de Mutsert, I.J. Deary, G. Dedoussis, E.W. Demerath, A.I. den Hollander, J.G. Dennis, E. Di Angelantonio, F. Drenos, M. Du, A.M. Dunning, D.F. Easton, T. Ebeling, T.L. Edwards, P.T. Ellinor, P. Elliott, E. Evangelou, A.E. Farmaki, J.D. Faul, M.F. Feitosa, S. Feng, E. Ferrannini, M.M. Ferrario, J. Ferrieres, J.C. Florez, I. Ford, M. Fornage, P.W. Franks, R. Frikke-Schmidt, T.E. Galesloot, W. Gan, I. Gandin, P. Gasparini, V. Giedraitis, A. Giri, G. Girotto, S.D. Gordon, P. Gordon-Larsen, M. Gorski, N. Grarup, M.L. Grove, V. Gudnason, S. Gustafsson, T. Hansen, K.M. Harris, T.B. Harris, A.T. Hattersley, C. Hayward, L. He, I.M. Heid, K. Heikkilä, Ø. Helgeland, J. Hernesniemi, A.W. Hewitt, L.J. Hocking, M. Hollensted, O.L. Holmen, G.K. Hovingh, J.M. Howson, C.B. Hoyng, P.L. Huang, K. Hveem, M.A. Ikram, E. Ingelsson, A.U. Jackson, J.H. Jansson, G.P. Jarvik, G.B. Jensen, M.A. Jhun, Y. Jia, X. Jiang, S. Johansson, M.E. Jørgensen, T. Jørgensen, P. Jousilahti, J.W. Jukema, B. Kahali, R.S. Kahn, M. Kähönen, P.R. Kamstrup, S. Kanoni, J. Kaprio, M. Karaleftheri, S.L. Kardia, F. Karpe, F. Kee, R. Keeman, L.A. Kiemeney, H. Kitajima, K.B. Kluivers, T. Kocher, P. Komulainen, J. Kontto, J.S. Kooner, C. Kooperberg, P. Kovacs, J. Kriebel, H. Kuivaniemi, S. Küry, J. Kuusisto, M. La Bianca, M. Laakso, T.A. Lakka, E.M. Lange, L.A. Lange, C.D. Langefeld, C. Langenberg, E.B. Larson, I.T. Lee, T. Lehtimäki, C.E. Lewis, H. Li, J. Li, R. Li-Gao, H. Lin, L.A. Lin, X. Lin, L. Lind, J. Lindström, A. Linneberg, Y. Liu, Y. Liu, A. Lophatananon, J. Luan, S.A. Lubitz, L.P. Lyytikäinen, D.A. Mackey, P.A. Madden, A.K. Manning, S. Männistö, G. Marenne, J. Marten, N.G. Martin, A.L. Mazul, K. Meidtner, A. Metspalu, P. Mitchell, K.L. Mohlke, D.O. Mook-Kanamori, A. Morgan, A.D. Morris, A.P. Morris, M. Müller-Nurasyid, P.B. Munroe, M.A. Nalls, M. Nauck, C.P. Nelson, M. Neville, S.F. Nielsen, K. Nikus, P.R. Njølstad, B.G. Nordestgaard, I. Ntalla, J.R. O'Connel, H. Oksa, L.M. Loohuis, R.A. Ophoff, K.R. Owen, C.J. Packard, S. Padmanabhan, C.N. Palmer, G. Pasterkamp, A.P. Patel, A. Pattie, O. Pedersen, P.L. Peissig, G.M. Peloso, C.E. Pennell, M. Perola, J.A. Perry, J.R. Perry, T.N. Person, A. Pirie, O. Polasek, D. Posthuma, O.T. Raitakari, A. Rasheed, R. Rauramaa, D.F. Reilly, A.P. Reiner, F. Renström, P.M. Ridker, J.D. Rioux, N. Robertson, A. Robino, O. Rolandsson, I. Rudan, K.S. Ruth, D. Saleheen, V. Salomaa, N.J. Samani, K. Sandow, Y. Sapkota, N. Sattar, M.K. Schmidt, P.J. Schreiner, M.B. Schulze, R.A. Scott, M.P. Segura-Lepe, S. Shah, X. Sim, S. Sivapalaratnam, K.S. Small, A.V. Smith, J.A. Smith, L. Southam, T.D. Spector, E.K. Speliotes, J.M. Starr, V. Steinthorsdottir, H.M. Stringham, M. Stumvoll, P. Surendran, 't Hart LM, K.E. Tansey, J.C. Tardif, K.D. Taylor, A. Teumer, D.J. Thompson, U. Thorsteinsdottir, B.H. Thuesen, A. Tönjes, G. Tromp, S. Trompet, E. Tsafantakis, J. Tuomilehto, A. Tybjaerg-Hansen, J.P. Tyrer, R. Uher, A.G. Uitterlinden, S. Ulivi, S.W. van der Laan, A.R. Van Der Leij, C.M. van Duijn, N.M. van Schoor, J. van Setten, A. Varbo, T.V. Varga, R. Varma, D.R. Edwards, S.H. Vermeulen, H. Vestergaard, V. Vitart, T.F. Vogt, D. Vozzi, M. Walker, F. Wang, C.A. Wang, S. Wang, Y. Wang, N.J. Wareham, H.R. Warren, J. Wessel, S.M. Willems, J.G. Wilson, D.R. Witte, M.O. Woods, Y. Wu, H. Yaghootkar, J. Yao, P. Yao, L.M. Yerges-Armstrong, R. Young, E. Zeggini, X. Zhan, W. Zhang, J.H. Zhao, W. Zhao, W. Zhao, H. Zheng, W. Zhou, EPIC-InterAct Consortium; CHD Exome+ Consortium; ExomeBP Consortium; T2D-Genes Consortium; GoT2D Genes Consortium; Global Lipids Genetics Consortium; ReproGen Consortium; MAGIC Investigators, J.I. Rotter, M. Boehnke, S. Kathiresan, McCarthy MI, C.J. Willer, K. Stefansson, I.B. Borecki, D.J. Liu, K.E. North, N.L. Heard-Costa, T.H. Pers, C.M. Lindgren, C. Oxvig, Z. Kutalik, F. Rivadeneira, R.J. Loos, T.M. Frayling, J.N. Hirschhorn, P. Deloukas, G. Lettre, Rare and low-frequency coding variants alter human adult height, Nature 542 (7640) (2017) 186–190.

[88] P.G. Murray, P.E. Clayton, S.D. Chernausek, A genetic approach to evaluation of short stature of undetermined cause, Lancet Diabetes Endocrinol. 6 (7) (2018 Jul) 564–574.

[89] A.D. Goddard, R. Covello, S.M. Luoh, T. Clackson, K.M. Attie, N. Gesundheit, A.C. Rundle, J.A. Wells, L.M. Carlsson, Mutations of the growth hormone receptor in children with idiopathic short stature. The Growth Hormone Insensitivity Study Group, N. Engl. J. Med. 333 (17) (1995) 1093–1098.

[90] E. Rao, B. Weiss, M. Fukami, A. Rump, B. Niesler, A. Mertz, K. Muroya, G. Binder, S. Kirsch, M. Winkelmann, G. Nordsiek, U. Heinrich, M.H. Breuning, M.B. Ranke, A. Rosenthal, T. Ogata, G.A. Rappold, Pseudoautosomal deletions encompassing a novel homeobox gene cause growth failure in idiopathic short stature and Turner syndrome, Nat. Genet. 16 (1) (1997) 54–63.

[91] S.R. Wang, C.M. Jacobsen, H. Carmichael, A.B. Edmund, J.W. Robinson, R.C. Olney, T.C. Miller, J.E. Moon, V. Mericq, L.R. Potter, M.L. Warman, J.N. Hirschhorn, A. Dauber, Heterozygous mutations in natriuretic peptide receptor-B (NPR2) gene as a cause of short stature, Hum. Mutat. 36 (4) (2015) 474–481.

[92] A. Hisado-Oliva, A. Ruzafa-Martin, L. Sentchordi, M.F.A. Funari, C. Bezanilla-López, M. Alonso-Bernáldez, J. Barraza-García, M. Rodriguez-Zabala, A.M. Lerario, S. Benito-Sanz, M. Aza-Carmona, A. Campos-Barros, A.A.L. Jorge, K.E. Heath, Mutations in C-natriuretic peptide (NPPC): a novel cause of autosomal dominant short stature, Genet. Med. 20 (1) (2018) 91–97.

[93] O.J. Dillon, S. Lunke, Z. Stark, A. Yeung, N. Thorne, Melbourne Genomics Health Alliance, Gaff C, White SM, Tan TY. Exome sequencing has higher diagnostic yield compared to simulated disease-specific panels in children with suspected monogenic disorders, Eur. J. Hum. Genet. 26 (5) (2018) 644–651.

[94] G.A. Vasques, A. Hisado-Oliva, M.F. Funari, A.M. Lerario, E.P. Quedas, P. Solberg, K.E. Heath, A.A. Jorge, Long-term response to growth hormone therapy in a patient with short stature caused by a novel heterozygous mutation in NPR2, J. Pediatr. Endocrinol. Metab. 30 (1) (2017) 111–116.

[95] G. Binder, G.A. Rappold, SHOX deficiency disorders, in: M.P. Adam, et al. (Ed.), GeneReviews((R)), 1993 Seattle (WA).

[96] M.B. Bober, G.A. Bellus, S.M. Nikkel, G.E. Tiller, Hypochondroplasia, in: M.P. Adam, et al. (Ed.), GeneReviews((R)), 1993 Seattle (WA).

[97] E.L. Wakeling, F. Brioude, O. Lokulo-Sodipe, S.M. O'Connell, J. Salem, J. Bliek, A.P. Canton, K.H. Chrzanowska, J.H. Davies, R.P. Dias, B. Dubern, M. Elbracht, E. Giabicani, A. Grimberg, K. Grønskov, A.C. Hokken-Koelega, A.A. Jorge, M. Kagami, A. Linglart, M. Maghnie, K. Mohnike, D. Monk, G.E. Moore, P.G. Murray, T. Ogata, I.O. Petit, S. Russo, E. Said, M. Toumba, Z. Tümer, G. Binder, T. Eggermann, M.D. Harbison, I.K. Temple, D.J. Mackay, I. Netchine, Diagnosis and management of Silver-Russell syndrome: first international consensus statement, Nat. Rev. Endocrinol. 13 (2) (2017) 105–124.

[98] C.R. Haldeman-Englert, A.C.E. Hurst, M.A. Levine, Disorders of GNAS Inactivation, in: M.P. Adam, et al. (Ed.), GeneReviews((R)), 1993 Seattle (WA).

[99] L.C.G. de Graaff, PROP1-related combined pituitary hormone deficiency, in: M.P. Adam, et al. (Ed.), GeneReviews((R)), 1993 Seattle (WA).

[100] K.S. Alatzoglou, M.T. Dattani, Genetic causes and treatment of isolated growth hormone deficiency-an update, Nat. Rev. Endocrinol. 6 (10) (2010) 562–576.

[101] J.E. Allanson, A.E. Roberts, Noonan syndrome, in: M.P. Adam, et al. (Ed.), GeneReviews((R)), 1993 Seattle (WA).

[102] I. Flechtner, K. Lambot-Juhan, R. Teissier, A. Colmenares, G. Baujat, J. Beltrand, Z. Ajaltouni, C. Pauwels, G. Pinto, D. Samara-Boustani, A. Simon, C. Thalassinos, M. Le Merrer, V. Cormier-Daire, M. Polak, Unexpected high frequency of skeletal dysplasia in idiopathic short stature and small for gestational age patients, Eur. J. Endocrinol. 170 (5) (2014) 677–684.

[103] Q. Fang, A.S. George, M.L. Brinkmeier, A.H. Mortensen, P. Gergics, L.Y. Cheung, A.Z. Daly, A. Ajmal, M.I. Pérez Millán, A.B. Ozel, J.O. Kitzman, R.E. Mills, J.Z. Li, S.A. Camper, Genetics of combined pituitary hormone deficiency: roadmap into the genome era, Endocr. Rev. 37 (6) (2016) 636–675.

[104] D.S. Millar, M.D. Lewis, M. Horan, V. Newsway, T.E. Easter, J.W. Gregory, L. Fryklund, M. Norin, E.C. Crowne, S.J. Davies, P. Edwards, J. Kirk, K. Waldron, P.J. Smith, J.A. Phillips 3rd, M.F. Scanlon, M. Krawczak, D.N. Cooper, A.M. Procter, Novel mutations of the growth hormone 1 (GH1) gene disclosed by modulation of the clinical selection criteria for individuals with short stature, Hum. Mutat. 21 (4) (2003) 424–440.

[105] M.J. Abuzzahab, A. Schneider, A. Goddard, F. Grigorescu, C. Lautier, E. Keller, W. Kiess, J. Klammt, J. Kratzsch, D. Osgood, R. Pfäffle, K. Raile, B. Seidel, R.J. Smith, S.D. Chernausek, Intrauterine Growth Retardation (IUGR) Study Group, IGF-I receptor mutations resulting in intrauterine and postnatal growth retardation, N. Engl. J. Med. 349 (23) (2003) 2211–2222.

[106] H.M. Domené, S.V. Bengolea, A.S. Martínez, M.G. Ropelato, P. Pennisi, P. Scaglia, J.J. Heinrich, H.G. Jasper, Deficiency of the circulating insulin-like growth factor system associated with inactivation of the acid-labile subunit gene, N. Engl. J. Med. 350 (6) (2004) 570–577.

[107] J. Pantel, M. Legendre, S. Cabrol, L. Hilal, Y. Hajaji, S. Morisset, S. Nivot, M.P. Vie-Luton, D. Grouselle, M. de Kerdanet, A. Kadiri, J. Epelbaum, Y. Le Bouc, S. Amselem, Loss of constitutive activity of the growth hormone secretagogue receptor in familial short stature, J. Clin. Invest. 116 (3) (2006) 760–768.

[108] L. Batey, J.E. Moon, Y. Yu, B. Wu, J.N. Hirschhorn, Y. Shen, A. Dauber, A novel deletion of IGF1 in a patient with idiopathic short stature provides insight into IGF1 haploinsufficiency, J. Clin. Endocrinol. Metab. 99 (1) (2014) E153–E159.

[109] G.A. Vasques, N. Amano, A.J. Docko, M.F. Funari, E.P. Quedas, M.Y. Nishi, I.J. Arnhold, T. Hasegawa, A.A. Jorge, Heterozygous mutations in natriuretic peptide receptor-B (NPR2) gene as a cause of short stature in patients initially classified as idiopathic short stature, J. Clin. Endocrinol. Metab. 98 (10) (2013) E1636–E1644.

[110] S.G. Kant, I. Cervenkova, L. Balek, L. Trantirek, G.W. Santen, M.C. de Vries, H.A. van Duyvenvoorde, M.J. van der Wielen, A.J. Verkerk, A.G. Uitterlinden, S.E. Hannema, J.M. Wit, W. Oostdijk, P. Krejci, M. Losekoot, A novel variant of FGFR3 causes proportionate short stature, Eur. J. Endocrinol. 172 (6) (2015) 763–770.

[111] J. Klammt, D. Neumann, E.F. Gevers, S.F. Andrew, I.D. Schwartz, D. Rockstroh, R. Colombo, M.A. Sanchez, D. Vokurkova, J. Kowalczyk, L.A. Metherell, R.G. Rosenfeld, R. Pfäffle, M.T. Dattani, A. Dauber, V. Hwa, Dominant-negative STAT5B mutations cause growth hormone insensitivity with short stature and mild immune dysregulation, Nat. Commun. 9 (1) (2018) 2105.

[112] N.T. Strande, E.R. Riggs, A.H. Buchanan, O. Ceyhan-Birsoy, M. DiStefano, S.S. Dwight, J. Goldstein, R. Ghosh, B.A. Seifert, T.P. Sneddon, M.W. Wright, L.V. Milko, J.M. Cherry, M.A. Giovanni, M.F. Murray, J.M. O'Daniel, E.M. Ramos, A.B. Santani, A.F. Scott, S.E. Plon, H.L. Rehm, C.L. Martin, J.S. Berg, Evaluating the clinical validity of gene-disease associations: an evidence-based framework developed by the clinical genome resource, Am. J. Hum. Genet. 100 (6) (2017) 895–906.

[113] J.M. Wit, M.B. Ranke, K. Albertsson-Wikland, A. Carrascosa, R.G. Rosenfeld, S. Van Buuren, B. Kristrom, E. Schoenau, L. Audi, A.C. Hokken-Koelega, P. Bang, H. Jung, W.F. Blum, L.A. Silverman, P. Cohen, S. Cianfarani, C. Deal, P.E. Clayton, L. de Graaff, J. Dahlgren, J. Kleintjens, M. Roelants, Personalized approach to growth hormone treatment: clinical use of growth prediction models, Horm. Res.

Paediatr. 79 (5) (2013) 257–270.
[114] B. Bakker, J. Frane, H. Anhalt, B. Lippe, R.G. Rosenfeld, Height velocity targets from the national cooperative growth study for first-year growth hormone responses in short children, J. Clin. Endocrinol. Metab. 93 (2) (2008 Feb) 352–357.
[115] P. Cohen, A.D. Rogol, C.P. Howard, G.M. Bright, A.M. Kappelgaard, R.G. Rosenfeld, American Norditropin Study Group, Insulin growth factor-based dosing of growth hormone therapy in children: a randomized, controlled study, J. Clin. Endocrinol. Metab. 92 (7) (2007 Jul) 2480–2486.
[116] P. Cohen, J. Germak, A.D. Rogol, W. Weng, A.M. Kappelgaard, R.G. Rosenfeld, American Norditropin Study Group, Variable degree of growth hormone (GH) and insulin-like growth factor (IGF) sensitivity in children with idiopathic short stature compared with GH-deficient patients: evidence from an IGF-based dosing study of short children, J. Clin. Endocrinol. Metab. 95 (5) (2010 May) 2089–2098.
[117] M.N. Pollak, E.S. Schernhammer, S.E. Hankinson, Insulin-like growth factors and neoplasia, Nat. Rev. Cancer 4 (7) (2004 Jul) 505–518.
[118] D.B. Allen, P. Backeljauw, M. Bidlingmaier, B.M. Biller, M. Boguszewski, P. Burman, G. Butler, K. Chihara, J. Christiansen, S. Cianfarani, P. Clayton, D. Clemmons, P. Cohen, F. Darendeliler, C. Deal, D. Dunger, E.M. Erfurth, J.S. Fuqua, A. Grimberg, M. Haymond, C. Higham, K. Ho, A.R. Hoffman, A. Hokken-Koelega, G. Johannsson, A. Juul, J. Kopchick, P. Lee, M. Pollak, S. Radovick, L. Robison, R. Rosenfeld, R.J. Ross, L. Savendahl, P. Saenger, H. Toft Sorensen, K. Stochholm, C. Strasburger, A. Swerdlow, M. Thorner, GH safety workshop position paper: a critical appraisal of recombinant human GH therapy in children and adults, Eur. J. Endocrinol. 174 (2) (2016 Feb) P1–P9.
[119] N.E. Bakker, R.J. Kuppens, E.P. Siemensma, R.F. Tummers-de Lind van Wijngaarden, D.A. Festen, G.C. Bindels-de Heus, G. Bocca, D.A. Haring, J.J. Hoorweg-Nijman, E.C. Houdijk, P.E. Jira, L. Lunshof, R.J. Odink, W. Oostdijk, J. Rotteveel, E.J. Schroor, A.A. Van Alfen, M. Van Leeuwen, E. Van Pinxteren-Nagler, H. Van Wieringen, R.C. Vreuls, N. Zwaveling-Soonawala, M.A. de Ridder, A.C. Hokken-Koelega, Eight years of growth hormone treatment in children with Prader-Willi syndrome: maintaining the positive effects, J. Clin. Endocrinol. Metab. 98 (10) (2013 Oct) 4013–4022.
[120] N.E. Bakker, J. van Doorn, J.S. Renes, G.H. Donker, A.C. Hokken-Koelega, IGF-1 levels, complex formation, and IGF bioactivity in growth hormone-treated children with Prader-Willi syndrome, J. Clin. Endocrinol. Metab. 100 (8) (2015 Aug) 3041–3049.
[121] O. Ali, P. Cohen, K.W. Lee, Epidemiology and biology of insulin-like growth factor binding protein-3 (IGFBP-3) as an anti-cancer molecule, Horm. Metab. Res. 35 (11 – 12) (2003 Nov-Dec) 726–733.
[122] P. Cohen, W. Weng, A.D. Rogol, R.G. Rosenfeld, A.M. Kappelgaard, J. Germak, Dose-sparing and safety-enhancing effects of an IGF-I-based dosing regimen in short children treated with growth hormone in a 2-year randomized controlled trial: therapeutic and pharmacoeconomic considerations, Clin. Endocrinol. 81 (1) (2014 Jul) 71–76.
[123] S. Malozowski, B.V. Stadel, Prepubertal gynecomastia during growth hormone therapy, J. Pediatr. 126 (4) (1995 Apr) 659–661.
[124] A.J. Swerdlow, R. Cooke, K. Albertsson-Wikland, B. Borgström, G. Butler, S. Cianfarani, P. Clayton, J. Coste, A. Deodati, E. Ecosse, R. Gausche, C. Giacomozzi, W. Kiess, A.C. Hokken-Koelega, C.E. Kuehni, F. Landier, M. Maes, P.E. Mullis, R. Pfaffle, L. Sävendahl, G. Sommer, M. Thomas, S. Tollerfield, G.R. Zandwijken, J.C. Carel, Description of the SAGhE cohort: a large European study of mortality and cancer incidence risks after childhood treatment with recombinant growth hormone, Horm. Res. Paediatr. 84 (3) (2015) 172–183.
[125] C.A. Sklar, A.C. Mertens, P. Mitby, G. Occhiogrosso, J. Qin, G. Heller, Y. Yasui, L.L. Robison, Risk of disease recurrence and second neoplasms in survivors of childhood cancer treated with growth hormone: a report from the Childhood Cancer Survivor Study, J. Clin. Endocrinol. Metab. 87 (7) (2002 Jul) 3136–3141.
[126] B. Ergun-Longmire, A.C. Mertens, P. Mitby, J. Qin, G. Heller, W. Shi, Y. Yasui, L.L. Robison, C.A. Sklar, Growth hormone treatment and risk of second neoplasms in the childhood cancer survivor, J. Clin. Endocrinol. Metab. 91 (9) (2006 Sep) 3494–3498.
[127] B.C. Patterson, Y. Chen, C.A. Sklar, J. Neglia, Y. Yasui, A. Mertens, G.T. Armstrong, A. Meadows, M. Stovall, L.L. Robison, L.R. Meacham, Growth hormone exposure as a risk factor for the development of subsequent neoplasms of the central nervous system: a report from the childhood cancer survivor study, J. Clin. Endocrinol. Metab. 99 (6) (2014 Jun) 2030–2037.
[128] S. Tamhane, J.G. Sfeir, N.E.N. Kittah, S. Jasim, W. Chemaitilly, L.E. Cohen, M.H. Murad, Growth hormone therapy in childhood cancer survivors: a systematic review and meta-analysis, J. Clin. Endocrinol. Metab. (2018 Jun 29), https://doi.org/10.1210/jc.2018-01205 (Epub ahead of print).
[129] J.C. Carel, E. Ecosse, F. Landier, D. Meguellati-Hakkas, F. Kaguelidou, G. Rey, Coste long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of the French SAGhE study, J. Clin. Endocrinol. Metab. 97 (2) (2012 Feb) 416–425.
[130] A.J. Swerdlow, R. Cooke, D. Beckers, B. Borgström, G. Butler, J.C. Carel, S. Cianfarani, P. Clayton, J. Coste, A. Deodati, E. Ecosse, R. Gausche, C. Giacomozzi, A.C.S. Hokken-Koelega, A.J. Khan, W. Kiess, C.E. Kuehni, P.E. Mullis, R. Pfaffle, L. Sävendahl, G. Sommer, M. Thomas, A. Tidblad, S. Tollerfield, L. Van Eycken, Zandwijken GRJ, Cancer risks in patients treated with growth hormone in childhood: the SAGhE European cohort study, J. Clin. Endocrinol. Metab. 102 (5) (2017 May 1) 1661–1672.
[131] L. Sävendahl, M. Maes, K. Albertsson-Wikland, B. Borgström, J.C. Carel, S. Henrard, N. Speybroeck, M. Thomas, G. Zandwijken, Hokken-Koelega. Long-term mortality and causes of death in isolated GHD, ISS, and SGA patients treated with recombinant growth hormone during childhood in Belgium, The Netherlands, and Sweden: preliminary report of 3 countries participating in the EU SAGhE study, J. Clin. Endocrinol. Metab. 97 (2) (2012 Feb) E213–E217.
[132] K. Albertsson-Wikland, A. Mårtensson, L. Sävendahl, A. Niklasson, P. Bang, J. Dahlgren, J. Gustafsson, B. Kriström, S. Norgren, N.G. Pehrsson, A. Odén, Mortality is not increased in recombinant human growth hormone-treated patients when adjusting for birth characteristics, J. Clin. Endocrinol. Metab. 101 (5) (2016 May) 2149–2159.
[133] M.O. Savage, P. Bang, The variability of responses to growth hormone therapy in children with short stature, Indian J. Endocrinol. Metab. 16 (Suppl. 2) (2012 Dec) S178–S184.
[134] P. Bang, S.F. Ahmed, J. Argente, P. Backeljauw, M. Bettendorf, G. Bona, R. Coutant, R.G. Rosenfeld, M.J. Walenkamp, M.O. Savage, Identification and management of poor response to growth-promoting therapy in children with short stature, Clin. Endocrinol. 77 (2) (2012 Aug) 169–181.
[135] P.E. Clayton, R.C. Cuneo, A. Juul, J.P. Monson, S.M. Shalet, M. Tauber, European Society of Paediatric Endocrinology. Consensus statement on the management of the GH-treated adolescent in the transition to adult care, Eur. J. Endocrinol. 152 (2) (2005) 165–170.
[136] D.M. Cook, K.C. Yuen, B.M. Biller, S.F. Kemp, M.L. Vance, American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth hormone use in growth hormone-deficient adults and transition patients – 2009 update, Endocr. Pract. 15 (Suppl. 2) (2009) 1–29.
[137] M.E. Molitch, D.R. Clemmons, S. Malozowski, G.R. Merriam, M.L. Vance, Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline, J. Clin. Endocrinol. Metab. 96 (6) (2011) 1587–1609.
[138] J.M. Garcia, B.M.K. Biller, M. Korbonits, V. Popovic, A. Luger, C.J. Strasburger, P. Chanson, M. Medic-Stojanoska, J. Schopohl, A. Zakrzewska, S. Pekic, M. Bolanowski, R. Swerdloff, C. Wang, T. Blevins, M. Marcelli, N. Ammer, R. Sachse, K.C.J. Yuen, Macimorelin as a diagnostic test for adult GH deficiency, J. Clin. Endocrinol. Metab. 103 (8) (2018 Aug 1) 3083–3093.
[139] L. Legeai-Mallet, C-type natriuretic peptide analog as therapy for achondroplasia, Endocr. Dev. 30 (2016) 98–105.
[140] J.S. Christiansen, P.F. Backeljauw, M. Bidlingmaier, B.M. Biller, M.C. Boguszewski, F.F. Casanueva, P. Chanson, P. Chatelain, C.S. Choong, D.R. Clemmons, L.E. Cohen, P. Cohen, J. Frystyk, A. Grimberg, Y. Hasegawa, M.W. Haymond, K. Ho, A.R. Hoffman, J.M. Holly, R. Horikawa, C. Höybye, J.O. Jorgensen, G. Johannsson, A. Juul, L. Katznelson, J.J. Kopchick, K.O. Lee, K.W. Lee, X. Luo, S. Melmed, B.S. Miller, M. Misra, V. Popovic, R.G. Rosenfeld, J. Ross, R.J. Ross, P. Saenger, C.J. Strasburger, M.O. Thorner, H. Werner, K. Yuen, Growth Hormone Research Society perspective on the development of long-acting growth hormone preparations, Eur. J. Endocrinol. 174 (6) (2016 Jun) C1–C8.
[141] K.C.J. Yuen, B.S. Miller, B.M.K. Biller, The current state of long-acting growth hormone preparations for growth hormone therapy, Curr. Opin. Endocrinol. Diabetes Obes. 25 (4) (2018 Aug) 267–273.