Guidelines

HORMONE RESEARCH IN PÆDIATRICS

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Towards a Rational and Efficient Diagnostic Approach in Children Referred for Growth Failure to the General Paediatrician

Jan M. Wit[a] Gerdine A. Kamp[b] Wilma Oostdijk[a] on behalf of the Dutch Working Group on Triage and Diagnosis of Growth Disorders in Children

[a]Department of Paediatrics, Leiden University Medical Center, Leiden, The Netherlands; [b]Department of Paediatrics, Tergooi Hospital, Blaricum, The Netherlands

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Short stature · Growth disorders · Turner syndrome · SHOX · NPR2 · IHH · ACAN · Microarray

Abstract
Based on a recent Dutch national guideline, we propose a structured stepwise diagnostic approach for children with growth failure (short stature and/or growth faltering), aiming at high sensitivity for pathologic causes at acceptable specificity. The first step is a detailed clinical assessment, aiming at obtaining relevant clinical clues from the medical history (including family history), physical examination (emphasising head circumference, body proportions and dysmorphic features) and assessment of the growth curve. The second step consists of screening: a radiograph of the hand and wrist (for bone age and assessment of anatomical abnormalities suggestive for a skeletal dysplasia) and laboratory tests aiming at detecting disorders that can present as isolated short stature (anaemia, growth hormone deficiency, hypothyroidism, coeliac disease, renal failure, metabolic bone diseases, renal tubular acidosis, inflammatory bowel disease, Turner syndrome [TS]). We advise molecular array analysis rather than conventional karyotyping for short girls because this detects not only TS but also copy number variants and uniparental isodisomy, increasing diagnostic yield at a lower cost. Third, in case of diagnostic clues for primary growth disorders, further specific testing for candidate genes or a hypothesis-free approach is indicated; suspicion of a secondary growth disorder warrants adequate further targeted testing.

Introduction

The diagnosis of children who are referred to a general paediatrician or paediatric endocrinologist for short stature and/or growth faltering (from now on termed growth failure [GF]) is difficult for multiple reasons. First, the many different causes of GF complicate the process of screening for pathologic conditions. Second, for most conditions little information is available about incidence and prevalence. Third, the phenotypic spectrum of each condition is insufficiently known, as is the percentage of cases that can present with isolated GF. Fourth, for each

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E-Mail karger@karger.com
www.karger.com/hrp

Prof. Dr. Jan M. Wit
Department of Paediatrics
Leiden University Medical Center, Albinusdreef 2
NL–2333 ZA Leiden (The Netherlands)
E-Mail j.m.wit@lumc.nl

condition, little information is available about the distribution of height SD score (HSDS); anecdotal information suggests considerable overlap with the population reference range. Fifth, the multitude of syndromes associated with GF makes it virtually impossible for the clinician to remember their phenotypes. Sixth, in the last 2 decades, several novel genetic causes have been discovered with a relatively high prevalence: up to 13% for copy number variants (CNVs) [1] and 1–2% for heterozygous defects of the Short Stature Homeobox gene (*SHOX*) [2], Natriuretic Peptide Receptor 2 gene (*NPR2*) [3–6], and the genes encoding aggrecan (*ACAN*) [7–9], Indian Hedge-Hog (*IHH*) [10] and Natriuretic Peptide Precursor C (Natriuretic Peptide, type C, *NPPC*) [11]. Most of these conditions were unknown to paediatricians at the time of their training, and there is still limited information about the respective phenotypic presentations. The fast development in this field has made most diagnostic algorithms in paediatric textbooks outdated.

A working group of the Paediatric Association of the Netherlands (4 paediatric endocrinologists, one representative each of general paediatrics, clinical genetics and primary youth health care) prepared a new guideline for practising general paediatricians on the diagnostic approach of children with GF and tall stature (2016–2018). Procedures are described in the online supplementary Information, pg 2–3 (for all online suppl. material, see www.karger.com/doi/10.1159/000499915). The present mini-review is based on the section on GF.

The main aim of this mini-review is to offer a guideline to the general paediatrician for a step-by-step diagnostic approach of the child referred for GF (Fig. 1). It starts with the child referred under the suspicion of being unusually short or growing unusually slowly (irrespective of the precise actual HSDS or recent HSDS change) or the child who develops abnormal growth during follow-up for another medical condition. The main reason for a relatively loose inclusion criterion is that many pathologic conditions can present with a growth curve within the normal range. For example, girls with Turner syndrome (TS) often have a normal height for population and target height (TH) in the first years of life [12], and some may have a height within the population range up to adolescence [13].

In the assessment of a child's individual growth curve, the clinician essentially aims at answering 3 questions: (1) how unusual is the child's height compared with the appropriate growth diagram?; (2) how unusual is the child's height compared with the height of the biological parents (expressed as TH)?; and (3) how unusual is the child's growth pattern over the foregoing years compared with the SD scores (SDS) lines (or centiles) on the growth chart? For background information about the choice of growth diagrams, various equations of TH and assessment of the growth curve, see online supplementary Information, pg 4–6.

Searching for Diagnostic Clues from Medical History, Physical Examination and Growth Curve

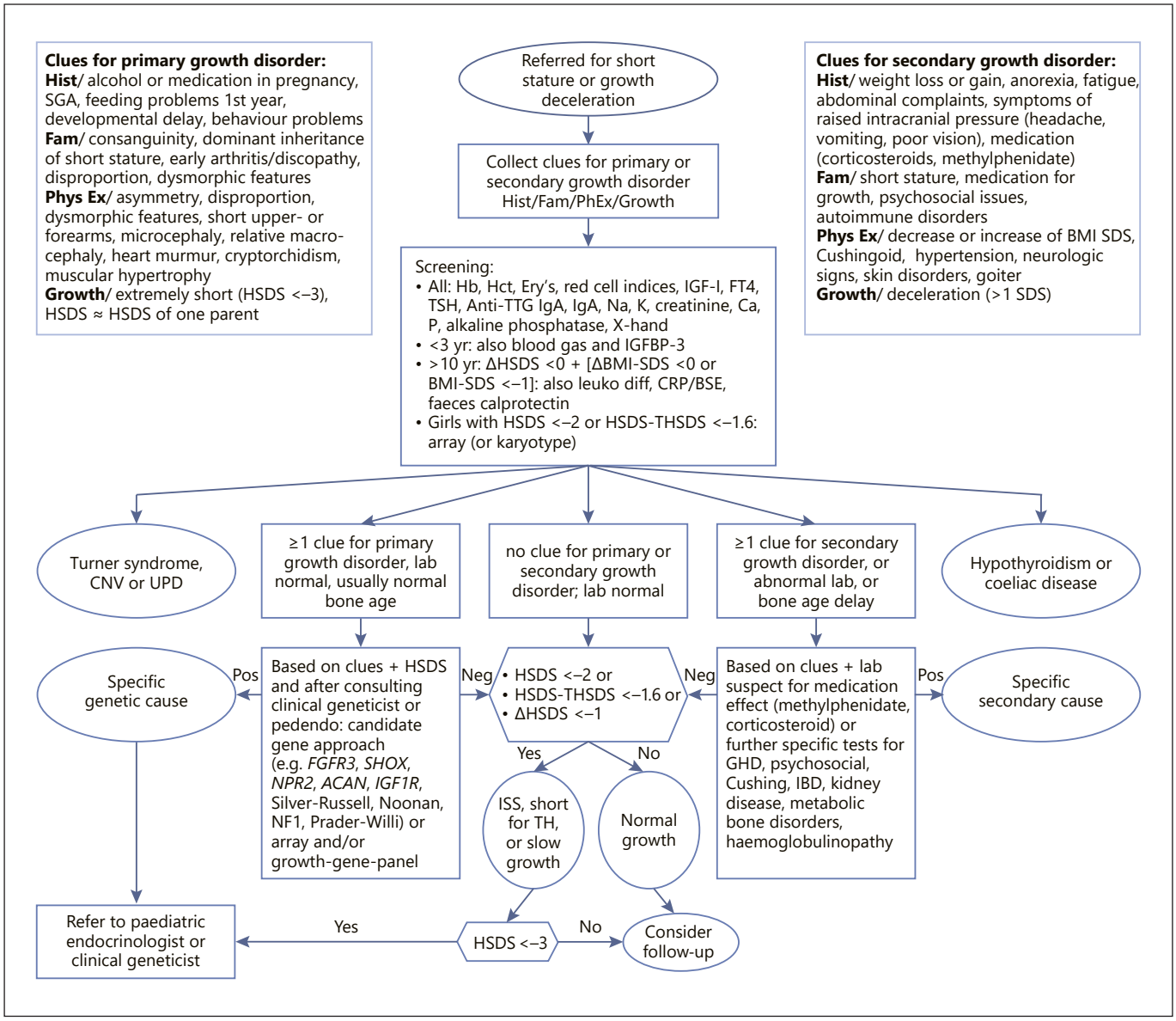
The Structure of the Diagnostic Flow Chart (Fig. 1)

The diagnostic flowchart starts with the child presenting at the clinic under the suspicion of GF. The clinician is expected to possess some general knowledge of the clinical features of the most relevant causes of GF. For a full list the reader is referred to the International Classification of Pediatric Endocrine Diagnoses [14]. Selected primary and secondary growth disorders that can present with few or atypical clinical features (apparent "isolated short stature") and with a relatively high incidence and clinical relevance are presented in online supplementary Tables 1 and 2, respectively, including the estimated incidence and prevalence in the population, the prevalence in children referred for short stature, and main clinical features.

The clinical assessment consists of a thorough medical history (including the family history), a detailed physical examination and analysis of the individual growth curve [15, 16], aimed at collecting diagnostic clues that point into the direction of a primary or secondary growth disorder.

The next step is a screening procedure consisting of an X-ray of the left hand/wrist and laboratory investigations. The X-ray should not only be investigated for skeletal age (bone age, BA) but also for anatomical abnormalities suggestive for a form of skeletal dysplasia [2–11, 17]. The latter purpose has become more important because of the recent discovery that heterozygosity for mutations in several genes known to be associated with various forms of severe skeletal dysplasia in homozygous carriers can present with few or nonspecific clinical features, but often do show radiological abnormalities.

The cumulative information from the clinical assessment and screening procedure should lead to a list of diagnostic clues for either a primary or a secondary growth disorder. Already in this screening phase, the diagnosis of several conditions can be established, such as TS, CNVs or uniparental disomy (UPD) in girls, and hypothyroidism, coeliac disease (CD) and iatrogenic disorders irre-



Color version available online

Fig. 1. Flowchart for the diagnostic approach of children referred for GF, or children who develop a growth disorder while attending the clinic for another medical reason. For explanation, see text. SGA, small-for-gestational age; HSDS, height SD score; Hb, haemoglobin; Hct, haematocrit; Anti-TTG IgA, anti-tissue transglutaminase IgA antibodies; BMI, body mass index; SDS, SD score; CNV, copy number variant; UPD, uniparental disomy.

spective of gender (Fig. 1). If the clinician identifies clues for a primary growth disorder, further genetic testing can be performed and when a form of skeletal dysplasia is suspected, a radiographic skeletal survey can be done [18]. If clues for a secondary growth disorder are present, targeted laboratory investigations are warranted, for example, a growth hormone (GH) stimulation test.

Diagnostic Categories

The 3 major categories of causes of GF are primary growth disorders (assumed to be due to disordered regulation of the epiphyseal growth plate), secondary growth disorders (assumed to be related to changes in external influences on the epiphyseal chondrocytes) and idiopathic short stature (ISS; for more information on ISS, see online suppl. Information pg 5–6), short for parental height

or slow growth of unknown origin [19, 20]. While the list of secondary growth disorders has hardly changed over the last decades, the number of primary growth disorders, which can present with mild, minor or even absent additional clinical features has considerably increased due to the expanding use of novel genetic techniques, in particular array analysis (Single Nucleotide Polymorphism microarray [SNP-array] or microarray-based comparative genomic hybridisation [CGH-array]) and whole exome sequencing (WES) [21–23]. Novel genetic causes of GF include heterozygous mutations of genes previously associated with skeletal dysplasias *(SHOX, NPR2, ACAN, IHH, NPPC)* [2–11] (online suppl. Table 1). The discovery of this group of conditions, all inherited in an autosomal dominant fashion, has also relevance for the questions to ask at history taking and even more for the clinical features the clinician should look for during the physical examination. Multiple recurrent CNVs (microdeletions and -duplications) have been associated with GF [24–27] at an average diagnostic yield of 13% [1], but usually children carrying such CNVs had some other clinical features as well.

Relevant Clues in the Medical History of a Child Referred for GF

On top of a standard full medical history, several questions related to specific features of several pathological causes should be added (specific questionnaire available on request). Examples of specific questions and interpretation of positive answers are shown in Table 1, and a part of these is also shown in Figure 1. Important clues for a primary growth disorder include increased alcohol consumption or medication in pregnancy, low birth weight and/or length (small-for-gestational age) [28], feeding problems or nutrition-related abnormalities (e.g., intolerance, avoidance) in the first year of life, developmental delay, intellectual disability and behavioural problems. Clues for secondary growth disorders include excessive or low weight gain, anorexia, fatigue, abdominal complaints, symptoms related to increased intracranial pressure and medication.

A thorough family history and a schematic pedigree are important components of the medical history, particularly for assessing the likelihood of a primary growth disorder. Consanguinity increases the risk of a recessive disorder, while one apparently affected parent increases the pre-test likelihood of an autosomal dominant condition [3–11]. A novel question to ask is whether there are adult family members affected by early-onset arthritis or discopathy (if positive, this increases the likelihood of a heterozygous *ACAN* mutation [7]). If one or both parents are short, special attention should be given to their body proportions and dysmorphic features.

The family history can also offer important information regarding the likelihood of a secondary growth disorder, for example, the presence of relatives with short stature (e.g., genetic forms of growth hormone deficiency [GHD]) [29], previous hormonal treatment, psychosocial issues and auto-immune disorders (familial occurrence increases the likelihood of juvenile hypothyroidism and CD).

Relevant Clues in the Physical Examination of a Child Referred for GF (online suppl. Table 3)

Anthropometry and Pubertal Status

Height, weight, head circumference, sitting height and arm span are essential measures and used to calculate SDS for age and sex. Body mass index (BMI) and sitting height/height ratio should be calculated and expressed as SDS. Pubertal status should be rated according to Tanner and can also be expressed as SDS [30–32].

Relative macrocephaly can point at Silver-Russell syndrome [33], 3M syndrome [34], neurofibromatosis 1 [35] and TS [36], while microcephaly is also an important clue for the differential diagnosis [22, 28]. In infants and toddlers, fontanelles and dentition should be evaluated [17].

A relatively high average sitting height/height ratio SDS is seen in most skeletal dysplasias and TS, while a decreased sitting height/height ratio SDS is observed in children with axial segment abnormalities [17], such as biallelic mutations of the gene encoding 3-prime-phosphoadenosine 5-prime-phosphosulfate synthase 2 (*PAPSS2*) [37]. Reference data for sitting height/height ratio are available in various countries [38–43]. Measuring sitting height is preferred above measuring lower segment because the latter has a relatively low accuracy and recent reference data for upper/lower segment ratio are scarce [44–47]. The relationship between arm span and height can be expressed as arm span minus height [47], arm span/height ratio [48] or arm span for height [49]. In most primary growth disorders, arm span is shorter than body height, except for heterozygous *ACAN* mutations [7].

The ratio between length of the upper arm and lower arm (and upper leg versus lower leg) is important for the differentiation between hypochondroplasia (short upper arms and legs, rhizomelia) versus *SHOX* or *NPR2* haploinsufficiency (short forearms and lower legs, mesomelia) [6, 48], although in hypochondroplasia short forearms have been reported [50].

Table 1. Special points of attention in the medical history of children with growth failure (0–18 years)*

Inquire about …	Interpretation
Reason of referral	
Previous growth data, growth pattern	A complete growth curve is essential for an adequate assessment of the growth disorders. Check for characteristic growth curves (e.g., for Turner syndrome). Increase of BMI SDS: Cushing, hypothyroidism, GH deficiency. Decrease of BMI SDS: IBD
Coping with short stature, bullying	Global evaluation of psychosocial consequences and coping
Pregnancy, delivery and early neonatal period	
Assisted reproduction, problems during pregnancy, for example intrauterine growth retardation, medication, intoxications (alcohol), infections	Assisted reproduction techniques are associated with methylation disturbances. If history is positive for alcohol abuse, check for foetal alcohol syndrome
Birth weight, length and head circumference (if unavailable, length and head circumference SDS within the first 3 months after birth can serve as proxy of birth measurements), duration of gestation (gestational age)	Compare with intrauterine growth charts and decide about SGA or AGA, and in case of SGA, proportionate or disproportionate. Note that 10% of SGA-born children do not catch-up in height. The *a priori* likelihood of a primary growth disorder is increased in SGA-born short children
Problems during and shortly after delivery (breech position, asphyxia, jaundice)	Pituitary deficiency is associated with breech delivery and prolonged jaundice. Postnatal hypoglycaemia is associated with GH deficiency or insensitivity, SGA, inborn errors of metabolism, etc.
Background data	
Delayed milestones, developmental delay, intellectual disability	Associated with many syndromes, chromosomal defects, metabolic disorders, etc.
Feeding problems in the first years of life	Silver-Russell syndrome (#180860), *IGF1R* defects (#270450), Prader-Willi syndrome (#176270), Noonan syndrome (#163950), Turner syndrome
Previous illnesses and operations, medication (e.g., inhalation steroids, methylphenidate), irradiation	Organic or iatrogenic causes. Irradiation can cause GH deficiency as well as growth restriction of the spine
Systems	
General (fatigue, energy)	Fatigue can be a symptom of anaemia, coeliac disease, IBD, chronic renal failure, hypothyroidism
Heart, lungs (energy, asthma, dyspnoea)	Fatigue and dyspnoea can be symptoms of cardiac failure or chronic lung disorders, including CF (#219700) and asthma
Gastro-intestinal (feeding, nutrition history, poor appetite, abdominal pain, diarrhoea, mouth ulcers, obstipation)	Fatigue, diarrhoea, poor appetite, abdominal distension, abdominal pain, mouth ulcers are suggestive for coeliac disease, malabsorption, IBD, CF and mitochondrial disorders
Urogenital system (micturition, infections)	Abnormal micturition or urinary tract infections can be associated with anatomical abnormalities or chronic kidney disorders
Endocrine (fatigue, slowness, constipation)	Hypothyroidism
CNS (headache, visual acuity, nausea, vomiting)	CNS associated symptoms lead to suspicion of a brain tumour
Nutrition (special diet, strange eating behaviour, underfeeding or overfeeding, intolerance or avoidance)	In case of failure to thrive make a detailed assessment of food intake. For toddlers and pre-schoolers, be alert of emotional deprivation. For adolescents: be alert of symptoms of anorexia nervosa or bulimia

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Table 1 (continued)

Inquire about …	Interpretation
Psychosocial aspects	
Social environment, functioning in school, type of school, learning achievements, social behaviour, physical activities, social contacts, personality, independence, vitality, mood, activities, sleep pattern, behaviour (mascotte, clownish, aggressive); unexplained physical complaints; attitude of the parents regarding physical growth	Check for symptoms of parental neglect, emotional deprivation, depression, anorexia nervosa Impression of parental concern and support, and adequacy of coping techniques of the child
Puberty	
All: presence and onset of pubic hair, axillary hair, acne or transpiration Girls: age at onset of breast development, age at menarche Boys: age at enlargement of penis and testis and at starting shaving (average 16 years)	Estimation of pubertal timing (early, normal, delayed). In case of delayed puberty, suspect GH deficiency, Noonan syndrome (#163950), constitutional delay of growth and puberty, etc.
Family history	
Country of origin of the parents, ethnicity	Determines which growth chart is to be used
Parental heights (preferably measured instead of reported)	Needed for calculation of target height. If height of one of the parents <-2 SDS, suspect dominant inheritance
Consanguinity	Increases probability of recessive genetic disorder
Start and tempo of maternal puberty (age at menarche) and paternal puberty (age at onset of pubic hair, growth spurt, shaving, delayed cessation of growth)	Influences probability of familial pattern of delayed puberty
Three generation pedigree, family history of similar cases, coeliac disease, auto-immune diseases, thyroid disorders, growth disorders, skeletal dysplasia, endocrine disorders, early-onset osteoarthritis or degenerative discopathy	Influences the probability of various genetic disorders associated with GF. Early osteoarthritis or degenerative discopathy is suspect for *ACAN* haploinsufficiency (#165800, #612921, #614205)

* For syndromes, MIM codes are added.

AGA, appropriate for gestational age; BMI, body mass index; CF, cystic fibrosis; CNS, central nervous system; GH, growth hormone; IBD, inflammatory bowel disease; SGA, small-for gestational age.

Dysmorphic Features

Special attention should be given to dysmorphic features, since these can offer clues for specific genetic conditions. Selected dysmorphic features are shown in online supplementary Table 3. For more details on dysmorphic features the reader is referred to the London Medical Database via www.Face2Gene.com [51] and a special issue of the Am J Medical Genetics containing 7 reviews on elements of morphology and standard terminology [52–58].

Features of Secondary Growth Disorders

The physical examination can also give important clues for a secondary growth disorder (Fig. 1, online suppl. Table 3). One of the best known examples is a high or recent increase of BMI SDS in combination with growth faltering, suspect of Cushing syndrome, hypothyroidism and GHD. Other examples include Cushingoid appearance (yearly school photographs may be helpful in such cases), hypertension, virilisation and striae in Cushing syndrome, neurologic abnormalities in acquired GHD, goitre in Hashimoto disease and skin disorders in CD. A low or decreasing BMI SDS in combination with growth faltering is a possible symptom for Crohn's disease [59–62], other chronic systemic illnesses or anorexia nervosa.

Interpretation of the Growth Curve

The clinician should be persevering in collecting as many as possible growth data from the foregoing years, in order to get a good picture of the growth curve. Several growth disorders are characterized by a specific growth pattern. For example, TS [12, 13, 63, 64], Noonan syndrome [65, 66] and probably also haploinsufficiency of *SHOX* [48], *NPR2* [6], *ACAN* [7], *IHH* [10] and *NPPC* [11] usually present with a growth curve starting with a low or low-normal birth length, decreasing length SDS for 2–3 years, followed by a stable HSDS in childhood and a further HSDS decrease during adolescence. An HSDS similar to the height of one of the parents obviously increases the likelihood of a dominant condition. It is plausible that a stable but extremely short stature (HSDS <–3) increases the likelihood of a primary growth disorder [21], while growth faltering is more compatible with severe GHD or GH insensitivity [29] or other secondary growth disorders.

Radiologic Investigations

Conventionally, an X-ray of the left hand and wrist is made in a child referred for GF for determination of skeletal age (bone age). This can either be done manually with an atlas [67, 68] or with an automated method [69]. In most primary growth disorders, bone age is close to chronological age. In children with heterozygous *ACAN* mutations, bone age is usually advanced [7], although later reports have shown that bone age can also be delayed [70, 71]. We suggest that an assessment of anatomical abnormalities be made by the radiologist. Several "novel" disorders can present with such abnormalities, summarized in Table 2. When a skeletal dysplasia is suspected, a skeletal survey is indicated [18], although presently an exome-based gene panel for skeletal dysplasias may be more efficient to establish a specific diagnosis [72].

Laboratory Screening

If the diagnostic clues from the clinical assessment suggest the presence of a specific diagnosis, targeted laboratory investigations should be performed. In the absence of any diagnostic clues, the standard recommendations in textbooks (e.g., [73–75]), practice guidelines [15, 16] and the ISS consensus statement [76] have been to perform laboratory screening to detect a subclinical chronic illness that initially can present as isolated GF. The diagnostic yield of most components of this screening procedure is probably very low in children without any abnormality in the clinical evaluation and with a normal growth velocity [77], but on the other hand, the clinician would not like to miss a clinically relevant diagnosis. This situation has led to a wide variation between paediatric practices [78, 79].

In the absence of experimental evidence supporting the use of any component of conventional laboratory screening, we tried to assess the pre-test probability of the presence of a chronic medical condition in a child referred for GF. After accepting the 8 priority conditions identified by a French interdisciplinary expert group [80] (CD, Crohn's disease, craniopharyngioma, juvenile nephronophtisis, TS, GHD with pituitary stalk interruption syndrome, infantile cystinosis and hypothalamic-optochiasmatic astrocytoma), we analysed the published results of studies on the diagnostic yield of laboratory screening (online suppl. Table 4), collected anecdotal evidence, assessed implications for treatment and follow-up, and estimated cost. The resulting list of laboratory investigations to perform in each child referred for GF, as well as investigations to be performed in specific subgroups, is shown in Table 3 and discussed in the following paragraphs.

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Table 2. Examples of anatomic abnormalities visible on an X-ray of the hand and wrist pointing at some relatively frequent growth disorders (alphabetical order)*

Growth disorder	Radiologic findings
3M syndrome (#273750)	Slender long bones
ACAN haploinsufficiency (#165800, #612921, #614205)	Brachydactyly in 5 out of 20 families; in 4 of these short thumbs were noted [7]
Albright hereditary osteodystrophy with multiple hormone resistance (pseudohypoparathyroidism, type Ia) (#103580)	Brachydactyly with shortening of metacarpals III, IV en V and the distal phalanx I in 70% of patients [174]
NPPC haploinsuffiency (*600296)	Small hands. The fourth metacarpal is slightly shorter and thinner than fifth and the first metacarpal is short and wide [11]
Hypophosphatasia (#600296)	Hypomineralization predominates at the metaphyses and epiphyses in the form of 'tongues' entering into the diaphyses, and consisting in areas of non-mineralized osteomalacic bone. The metaphyses may also look like spurs [175]
IHH haploinsufficiency (#112500)	Abnormal hand radiographs in 6 of 12 children. Two children presented only shortening of the middle phalanx of the fifth finger. Other radiological hand findings include varying degrees of shortening of the middle phalanx of the second and fifth fingers with cone-shaped epiphyses [10]
NPR2 haploinsufficiency (#616255)	As in *SHOX* defects, except for Madelung deformity [3, 6]
Osteogenesis imperfecta (multiple MIM entries)	Osteopenia (cortical bone thinning and excessive trabecular bone transparency) and fractures [176]
Rickets (vitamin D deficiency, X-linked hypophosphataemic rickets; multiple MIM entries)	Loss of the zone of provisional calcification at metaphyses and around secondary growth centres, lack of the metaphyseal collar of Laval-Jeantet or delayed enchondral ossification. If secondary hyperparathyroidism: more prominent than normal trabeculae in the tubular bones, washed-out or indistinct bone cortex [177, 178]
SHOX (enhancer) haploinsufficiency (#300582)	*Hand and wrist:* Madelung deformity, carpal wedging (pyramidisation of the carpal row), decreased carpal angle, abnormal shape of distal radial epiphysis (flat, round, convex, triangular or trapezoidal), metaphyseal lucency and epiphyseal hypoplasia at the ulnar border of the distal radius, subluxation of the distal ulna, short 4th and/or 5th metacarpals. In doubt also make X-ray of forearm *Forearm:* mesomelic shortening of the total length of the radius (short forearm), lateral and dorsal radial bowing, ulnar bowing and elbow deformities (e.g., abnormal projection of the radial head vs. the proximal ulna), degree of ulnar variance (angle drawn from lines tangential to the distal surfaces of the radius and ulna, reflecting disparity between the lengths of the ulna and radius), subluxation of ulnar head, radial length and ulnar length, angulation of the distal radius and ulna [179, 180]
Turner syndrome	Short metacarpal IV (35%), Madelung deformity (5%) [145]

* For syndromes, MIM codes are added.

Table 3. Laboratory screening for children referred for growth failure

Patients	Laboratory determinations	Purpose (indicates/confirms/excludes)
All	Hb, Hct, erythrocytes, red cell indices	Anaemia (hemoglobinopathies, coeliac disease, IBD, other chronic diseases)
	IGF-I	GH deficiency or insensitivity, IGF insensitivity
	TSH, FT4	Hypothyroidism
	anti-TTG IgA, total IgA	CD
	Na, K, creatinine, Ca, P, alkaline phosphatase**	Kidney insufficiency, metabolic bone disorders
Girls with a height SDS <–2 SDS and/or >1.6 SD shorter than THSDS	Genetic investigation of chromosomal disorders (in particular Turner syndrome) with (preferably) array analysis or karyotyping*	Turner syndrome. With CGH-array also CNVs can be detected. With SNP-array also CNVs and uniparental isodisomy can be detected.
<3 years, growth faltering	Blood gas analysis, serum IGFBP-3	Renal tubular acidosis, GH deficiency
≥10 years, growth faltering and decreasing or low BMI SDS (<–1)	ESR or CRP, leukocytes, leukocyte differentiation. Calprotectin in stools	IBD, in particular Crohn's disease

* In girls with clinical suspicion of Turner syndrome with negative result of first line genetic testing (array analysis or karyotyping) a FISH test can be performed on a buccal swab, saliva or urine.

** Basic and comprehensive metabolic panels are bundled in some hospitals and can be less expensive than individual tests.

Hb, haemoglobin; Hct, haematocrit; IBD, inflammatory bowel disease; anti-TTG IgA, anti-tissue transglutaminase IgA antibodies; CD, Coeliac disease; Na, sodium; K, potassium; Ca, calcium; P, phosphate; CNV, copy number variant.

Laboratory Investigations in All Children Referred for GF

Haematology (Haemoglobin, Haematocrit, Erythrocytes, Red Cell Indices)

Anaemia (decreased haemoglobin [Hb] concentration), with or without abnormalities in haematocrit and red cell indices (mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration and red cell distribution width) can be an indicator of a chronic illness, iron deficiency, haemoglobinopathy (e.g., thalassaemia, sickle cell anaemia), CD or inflammatory bowel disease (IBD).

Thalassaemia and sickle cell anaemia are in almost all cases limited to individuals of Mediterranean, African or Asian origin and can be associated with GF [81, 82]. Usually the diagnosis is already known before GF is apparent. If a form of haemoglobinopathy is suspected in a child belonging to a population at risk, serum iron and ferritin as well as Hb electrophoresis can be added [83].

Serum Insulin-Like Growth Factor (IGF-I)

While children with severe congenital GHD usually can be diagnosed clinically at an early age based on typical clinical features shortly after birth and a rapid onset of decreasing HSDS [29], children with less severe idiopathic isolated GHD have a more variable growth pattern, which is difficult to distinguish from late maturing children. They can even show a growth pattern characterized by several years of growth faltering followed by stable but low HSDS, particularly if TH is relatively high [84]. Acquired GHD is usually caused by cranial tumours or other space occupying lesions, or their treatment modalities, and usually presents with growth faltering [85] in combination with increasing BMI SDS.

GHD is one of the most frequently detected diagnoses in children with isolated GF (online suppl. Table 4). The diagnosis of idiopathic isolated GHD contains almost always an element of uncertainty and we therefore prefer to assign a degree of likelihood of GHD based on clinical features, growth pattern, delayed bone age, serum IGF-I and insulin-like growth factor binding protein 3 (IGFBP-3), exclusion of other causes and the serum GH response to 2 stimulation tests (only in the first week of life single random GH levels can be used for the diagnosis [86]). If GHD is considered sufficiently likely, GH treatment can be started. The key element of the diagnosis – the maximum serum GH during 2 GH stimulation tests – is known to have a low specificity [17, 76, 87], so that false-positive re-

sults can easily occur [88–90]. We appreciate that one of the unresolved issues in the literature is the use of sex steroid priming prior to stimulation tests [17, 90–94], but believe that priming is needed in prepubertal children (in our country from 8 [girls] or 10 [boys] years onwards) to limit the percentage of false-positive results.

Serum IGF-I is commonly used as a screening parameter [95, 96] with an average positive and negative likelihood ratio of 2.5 and 0.5, respectively [97]. The interpretation of serum IGF-I is dependent on the assay [98], availability of adequate reference diagrams enabling conversion to SDS for age, sex and pubertal stage, attention to other factors influencing IGF-I concentration (nutritional status, liver function, thyroid function and pubertal stage) [96, 99–101] and the a priori likelihood of GHD based on clinical information (balance of positive and negative clues from medical history, physical examination and growth analysis). If IGF-I SDS is >0, GHD is unlikely.

Studies on the potential additive value of serum IGFBP-3 determinations at the screening stage are contradictory [97, 102–106], except for infants and young toddlers [76, 96, 107, 108]. We advise to repeat a baseline measurement of IGF-I and add an IGFBP-3 determination when a GH stimulation test is carried out, except in children <3 years, where IGFBP-3 can better be added even in the screening phase [76, 96].

The results of serum IGF-I and IGFBP-3 can also suggest other defects in the GH-IGF-I axis. Low IGF-I and IGFBP-3 in combination with a normal or elevated GH peak on stimulation is an indicator of either bioinactive GH (Kowarski syndrome) or one of the forms of GH insensitivity (caused by mutations of *GHR*, *STAT5B*, *STAT3*, *IGFALS* or *IGF1*) [22, 109]. In such cases, an IGF-I generation test can be useful, despite its limitations [110–113]. A serum IGF-I in the upper half of the normal range or higher is consistent with a heterozygous mutation or deletion of *IGF1R* [114], bi-allelic defect of *PAPPA2* [115] or a form of Silver-Russell syndrome, including *IGF2* defect [116].

FT4, TSH

In countries where no neonatal screening for congenital hypothyroidism is performed, postnatal GF is an important clue to the diagnosis. Neonatal screening based on thyroid stimulating hormone (TSH) determination can only detect primary hypothyroidism, while the combination of thyroxine (T4) and TSH screening detects both primary and secondary hypothyroidism [117].

Acquired juvenile hypothyroidism is rare, particularly below 10 years of age, and usually caused by Hashimoto thyroiditis. A positive family history for acquired autoimmune thyroid disorders and an increasing BMI SDS in combination with growth faltering are important diagnostic clues. It can take several years before HSDS gets below –2, depending on THSDS [118, 119]. Treatment with L-thyroxine leads to almost instantaneous normalisation of the symptoms and signs and to a fast catch-up growth [118, 119].

Anti-Anti-Tissue Transglutaminase IgA Antibodies and Total IgA

Arguments in favour of determining anti-tissue transglutaminase IgA antibodies and total IgA for screening of CD include the high incidence in the population (on average 0.7% of the world population) [120] and a high diagnostic yield in children with GF (2–15%) [121–128]. However, most children diagnosed with CD have a height within the normal range (mean HSDS at presentation –0.5 SDS [129]) and only a tiny average decrease of HSDS (0.07 SDS/year) in the first 2 years of life [130].

Obviously, the chance of finding CD is greater if one or more of the typical characteristics of CD are present, such as distended abdomen, abnormal defaecation pattern, fatigue, anorexia, anaemia, skin disorders (e.g., dermatitis herpetiformis), mouth ulcers, and so on (Table 1, online suppl. Table 3) [126]. Laboratory screening should be performed in any child referred for GF, irrespective of current HSDS or its deflection [129]. The determination of anti-tissue transglutaminase IgA plus total IgA has sufficient sensitivity [131, 132]. If there is clinical suspicion of CD, one can consider additional determination of anti-endomysium antibodies. In case of IgA deficiency, IgG antibodies should be tested.

Na, K, Creatinine

Growth faltering can be the first sign of a chronic kidney disease [80, 133], such as infantile cystinosis (median age at diagnosis 18–21 months) [134–138] and juvenile nephronophthisis (mean [SD] age at diagnosis 9.3 [3.0] years) [139]. Screening for urinary glucose, protein, blood and sediment does not have an additive value.

Serum Ca, P, and Alkaline Phosphatase

In theory, several disorders of calcium-phosphate metabolism (e.g., vitamin D deficiency [rickets], hypophosphatasia, hypophosphataemic rickets, [pseudo]hypoparathyroidism and osteogenesis imperfecta) can be associated with isolated GF [22, 140], but their low prevalence and usually present additional clinical features render the pre-test probability very low. We have not found reports

showing that isolated GF can be the presenting sign of any of these disorders, but we collected anecdotal information indicating that this can occur, so that we decided to keep these determinations in the screening panel.

Laboratory Investigations with Insufficient Evidence to Be Included into the Screening Panel

In contrast to most textbooks and reviews (e.g., [15–17, 76]), we have omitted the determination of thrombocyte and leukocyte counts, leukocyte differentiation and erythrocyte sedimentation rate or C-reactive protein, liver function tests and urine analysis from laboratory screening. However, if the liver is enlarged at physical examination or if a metabolic disorder is suspected for other reasons, liver function tests, serum cholesterol, triglycerides, uric acid and a comprehensive metabolic panel should be considered.

Additional Laboratory Investigation in Children <3 Years: Blood Gas and Serum IGFBP-3

A retrospective study on growth and age at diagnosis of children with renal tubular acidosis [141] showed that they can indeed present with isolated growth faltering, but almost always before the age of 3 years [15]. We therefore maintain our advice to limit blood gas testing to children below 3 years. As mentioned earlier, serum IGFBP-3 is useful as screening parameter for GHD in this age group.

Additional Laboratory Investigations in Teenagers (>10 Years) who Present with Growth Faltering and Decreasing BMI or a BMI SDS <–1: Leukocyte Count and Differentiation, Faecal Calprotectin

One of the priority target conditions for growth monitoring [80] is IBD, particularly Crohn's disease. While IBD usually presents with a combination of intestinal complaints (e.g., abdominal pain, diarrhoea, weight loss, and in patients with colitis ulcerosa also rectal blood loss) and growth faltering [142], the latter can also occur before the onset of gastro-intestinal symptoms [59–62, 143], usually in combination with a low or decreasing BMI SDS [59, 80].

We advise to specifically collect information on intestinal complaints (e.g., abdominal pain, blood and mucus in the stool and fatigue) at history taking (Table 1), but speculate that this may not be sufficient to diagnose all children with IBD at an early stage. Therefore, laboratory screening (leukocyte count, leukocyte-differentiation, one or both inflammation parameters [erythrocyte sedimentation rate and/or C-reactive protein] and determination of faecal calprotectin) in teenagers with an a priori increased risk appears indicated, that is, in those ≥10 years with GF and a decreased or decreasing BMI SDS. Since IBD can also (but rarely) occur at a younger age, these laboratory tests can also be considered in young children with such pattern of linear growth and BMI SDS.

Additional Testing in All Girls Referred for GF with a HSDS <–2 AND/OR a Height 1.6 SD Below THSDS

TS is a well-known and relatively frequent cause of short stature in girls (online suppl. Table 1), but the average age at diagnosis is still late [64, 144]. Timely diagnosis of TS enables early detection and management of concomitant anatomical disorders, for example, coarctation of the aorta, abnormal aorta valves and anatomical abnormalities of the urogenital system [145]. Further, timely diagnosis enables early treatment with GH, which increases adult height gain [146].

Usually one or more of the characteristic Turner stigmata are present in girls with TS [145], but 2–3% present with apparent isolated GF [147, 148]. HSDS can be within the normal range (mean HSDS ranges from –2.8 to –2.2 with an SD of approximately 1.0 [149–151]) and growth monitoring criteria have a sensitivity of 52–75% for TS [150, 152–154]. The pre-test probability of TS in a girl with apparent isolated GF is higher in the presence of a specific growth pattern (mean birth length SDS –0.7, fast decrease of HSDS in the first year [to –1.6 SDS] followed by a more gradual decrease at 2 and 3 years, a stable or slightly decreasing HSDS up to 10 years and an absent pubertal growth spurt [12, 13]), a low birth length [36, 155–157], a large distance between HSDS and THSDS (>2) [149, 152, 156], a relatively high sitting height/height ratio [151]), normal head circumference [36, 158, 159] and pubertal delay or primary amenorrhoea [156].

Traditionally, serum LH and FSH have been determined to estimate the likelihood of TS, but the diagnostic value is limited to girls of 0–2 years of age or in girls ≥10 years, and even in those age ranges, false-negative results are not rare [160].

While karyotyping has been the standard genetic technique for detecting TS, and still advised in the recent consensus on TS [145], we favour array analysis (SNP-array or CGH-array) because of the following reasons: (1) Similar sensitivity for virtually all TS variants [161]; (2) possibility to diagnose other chromosomal aberrations (e.g., XY/X) and CNVs (microdeletions and -duplications) at other chromosomal locations related to growth; (3) if a SNP-array is used, also most forms of uniparental isodisomy can be detected [162]; and (4) lower cost because

the assay is less labour-intensive. Thus, the high "number needed to test" (≈40) using karyotyping in girls with isolated GF [147, 148] can be considerably decreased by using SNP arrays, which can detect CNVs in up to 13% [1, 22, 24–27] and UPDs. However, there are also disadvantages of array analysis, such as the identification of a CNV of uncertain significance or of "susceptibility loci," which may lead to further testing of the patient and parents.

Since a large distance between HSDS and THSDS is a better predictor for TS than a low HSDS [149, 152] and girls with TS can have a height within the normal range, we propose genetic testing for TS in girls if HSDS <–2 OR >1.6 SD below THSDS. If in a girl with high clinical suspicion of TS the array analysis or karyotype yields a normal result, a FISH Y/X can be performed, preferably in another tissue (e.g., a buccal smear or urinary sample).

Preliminary Decision on Likelihood of Primary or Secondary Cause Followed by Further Testing

After collecting diagnostic clues from the medical history, physical examination, growth analysis and radiological and laboratory screening, 5 diagnoses can be made: hypothyroidism, CD, TS, or a known pathogenic CNV or UPD in girls (Fig. 1). If none of these disorders have been found, the paediatrician should estimate the likelihood of a primary growth disorder or a secondary growth disorder based on the collection of diagnostic clues. Further diagnostic steps are dependent of this estimation.

Diagnostic Approach if ≥1 Clue for a Primary Growth Disorder

If some form of primary growth disorder appears likely, we suggest that the general paediatrician designs the further diagnostic approach in collaboration with a clinical geneticist or paediatric endocrinologist. In boys, and in girls in whom karyotyping was used for genetic screening for TS, it would be logical to first consider array analysis [1, 23, 109, 163]. If negative, one can decide on a candidate gene approach if the child is disproportionate and/or shows dysmorphic features that are typical of one of the established genetic causes of short stature (online suppl. Table 1).

However, the phenotypic profiles of various genetic disorders show considerable overlap (e.g., similar clinical features of children with *SHOX* and *NPR2* haploinsufficiency [6], and in children with mild or absent physical signs unpredicted mutations in multiple genes can be found [9, 23, 164]). Therefore, a WES-based, growth-specific gene panel ("singleton WES with targeted phenotype-driven analysis" [72]) may be a more cost-effective approach [23, 72, 165–169] (for a detailed flowchart, see [23]). Sanger sequencing or WES (with present technology) can only diagnose mutations (including very small deletions and splicing defects), but not larger deletions within or around the gene, so that for the diagnosis of *SHOX* haploinsufficiency usually first a specific multiplex ligation-dependent probe amplification (MLPA) test [170] is performed to detect deletions or duplications of exons and gene enhancers, if normal followed by Sanger sequencing [2, 171]. MLPA tests are available for a large number of genes.

If singleton WES in the child does not lead to a diagnosis, a trio WES can be considered (i.e., WES on DNA from patient and both parents), which may lead to the diagnosis of unexpected known or novel conditions [9, 21, 22]. If this is negative, further testing can be discontinued, until future techniques become available for clinical use (e.g., RNA sequencing, methylation arrays and whole genome sequencing [172]).

Establishing the diagnosis can have important consequences for treatment decisions, for example, withholding GH treatment in cancer predisposition conditions (e.g., Bloom syndrome, Fanconi anaemia) [173], additional assessment of possible comorbidities and genetic counselling.

Diagnostic Approach if ≥1 Clue for a Secondary Growth Disorder

If some form of secondary growth disorder seems likely, one can either establish a diagnosis based on medical history alone, – for example, effect of medication (methylphenidate, steroids), anorexia nervosa, or psychosocial dwarfism – or perform further specific testing for other conditions. If clinical features, growth pattern and serum IGF-I suggest GHD, 2 GH stimulation tests, serum IGFBP-3 and a repeat serum IGF-I are indicated, and followed by a brain MRI if GHD is diagnosed [90, 95].

Approach if There Are No Clues for Any Specific Growth Disorder, or Negative Results of Evaluation of Primary and Secondary Causes

In the absence of any diagnostic clues, or if further testing is negative, the next step is dependent on the degree of abnormality of the growth pattern. If HSDS <–2, one can apply the diagnostic label ISS, either familial or non-familial. If height is in the lower normal range but >1.6 SDS shorter than THSDS, one can call this "short for TH of unknown origin." If HSDS and HSDS-THSDS are still in

the normal range but growth is slow in a fully asymptomatic child, most clinicians would like to make a follow-up appointment. In extreme cases, for example if HSDS <–3, we suggest to refer the child to a specialized growth centre. We advise to keep track of severely short patients in whom no cause could be found with current technology, and to consider the application of novel forms of (epi)genetic testing when these become available.

Conclusions

The recent discovery of a number of novel genetic disorders associated with GF has not only changed its differential diagnosis but also has consequences for the content of the medical history, physical examination, assessment of the growth curve, radiological assessment and laboratory screening. We propose a stepwise diagnostic approach, consisting of collecting diagnostic clues for a primary or secondary growth disorder, radiological and laboratory screening, interpretation of the clues and screening results, and if indicated, further genetic or biochemical testing. The relatively high prevalence of dominant genetic causes of GF with subtle dysmorphic features and mild body disproportion emphasises the need of a thorough search for dysmorphisms and of including head circumference, sitting height and arm span measurements into the physical examination. SNP-arrays and exome-based growth-specific gene panels are useful tools if a primary growth disorder is suspected.

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Dutch Working Group on Triage and Diagnosis of Growth Disorders in Children

Other members include Boudewijn Bakker (Department of Paediatrics, University Medical Center Utrecht, Utrecht, the Netherlands), Sarina G. Kant (Department of Clinical Genetics, Leiden University Medical Center, Leiden, the Netherlands), Roelof J. Odink (Department of Paediatrics, Catharina Hospital, Eindhoven, and Department of Paediatrics, Máxima Medical Centre, Eindhoven, The Netherlands), and Jeroen A. de Wilde (Department of Primary Health Care, Leiden University Medical Center, Leiden, the Netherlands).

Statement of Ethics

The authors have no ethical conflicts to disclose.

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Author Contributions

J.M.W. was one of the 2 leading authors of the Dutch guideline and took the lead in writing the manuscript. W.O. chaired the Committee responsible for the guideline and was involved in all subsequent versions of the guideline and the manuscript. G.A.K. was member of the Committee and revised multiple versions of the guideline and manuscript. All authors and members of the Committee agree with the submitted manuscript.

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