Etiologies and Early Diagnosis of Short Stature and Growth Failure in Children and Adolescents

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Accurate measurement of height and weight using standardized techniques is a fundamental component of pediatric medical visits. Calculation of height velocity over time enables comparison with standardized growth charts to identify potential deviations from normal. Growth deviations may be expressed as SD from the normal population mean for children of comparable age and sex; children with heights >2 SD below the mean are generally classified as short stature. In a child with suspected impaired growth, a detailed evaluation should be conducted to identify the cause. Such an evaluation may include a combination of personal, family, and social history; physical examination; general and perhaps specialized laboratory evaluations; radiologic examinations; genetic testing; and consultation with a pediatric subspecialist, such as a pediatric endocrinologist. Variants of normal growth include familial short stature, constitutional delay of growth and puberty, and small for gestational age with catch-up growth. Pathological causes of abnormal growth include many systemic diseases and their treatments, growth hormone deficiency, and a series of genetic syndromes, including Noonan syndrome and Turner syndrome. Children with short stature in whom no specific cause is identified may be diagnosed with idiopathic short stature. Early identification of abnormal growth patterns and prompt referral to specialist care offer children with growth failure and/or short stature the greatest chance for appropriate diagnosis, treatment, and improved clinical outcomes. *(J Pediatr 2014;164:S1-S14)*.

Auxology is the science of growth and development. For the practicing pediatrician, auxology is applied in the evaluation and measurement of growth through widely validated clinical methods, used daily for the evaluation of normal child maturation and identification of deviations from normal. Measuring length or height, weight, and head circumference in infants and younger children is a fundamental component of pediatric medical visits, allowing for the early identification of growth alterations or abnormalities potentially associated with concomitant treatable conditions or known genetic syndromes.[1] Proper measurement techniques must be used consistently. Subsequent plotting of measurements on appropriate growth charts with careful monitoring and interpretation of changes over time may ensure prompt specialist referral for children with growth abnormalities.[1-4] Such childhood growth abnormalities may manifest as slow or excessive gains in height, weight, or both. In this report, we focus on the diagnostic evaluation of children with short stature owing to any of a variety of causes.

How to Measure Growth

Key evaluations used to determine growth in children over time include measurements of length or height, weight, and head circumference.[1,3] Determination of the circumference of the waist, hips, and neck and measurement of skin folds may provide additional information on growth in selected children.

Length is usually the measurement of choice in children aged <2 years, and height is the standard measurement for children aged >3 years.[3] Between 2 and 3 years of age, both measurements often are recorded to allow comparison with previous length measurements and to provide new reference values for assessment of later increases in height. The importance of proper technique when measuring length and/or height cannot be overstated. Ideally, infants are measured for length in a firm box with an inflexible board and fixed headboard, and children are measured for height while standing erect against a wall-mounted stadiometer. Tips to help ensure accurate length and height measurements are provided in **Figure 1**. Both length and height should be recorded to

BMI	Body mass index	MGRS	Multicenter Growth Reference Study
CDC	Centers for Disease Control and Prevention	MPH	Midparental height
		NS	Noonan syndrome
CDGP	Constitutional delay of growth and puberty	PE	Physical examination
		PWS	Prader-Willi syndrome
GH	Growth hormone	SGA	Small for gestational age
GHD	Growth hormone deficiency	SHOX	Short stature homeobox
HV	Height velocity	TH	Target height
IGF-1	Insulin-like growth factor 1	TS	Turner syndrome
ISS	Idiopathic short stature	WHO	World Health Organization
IUGR	Intrauterine growth restriction		

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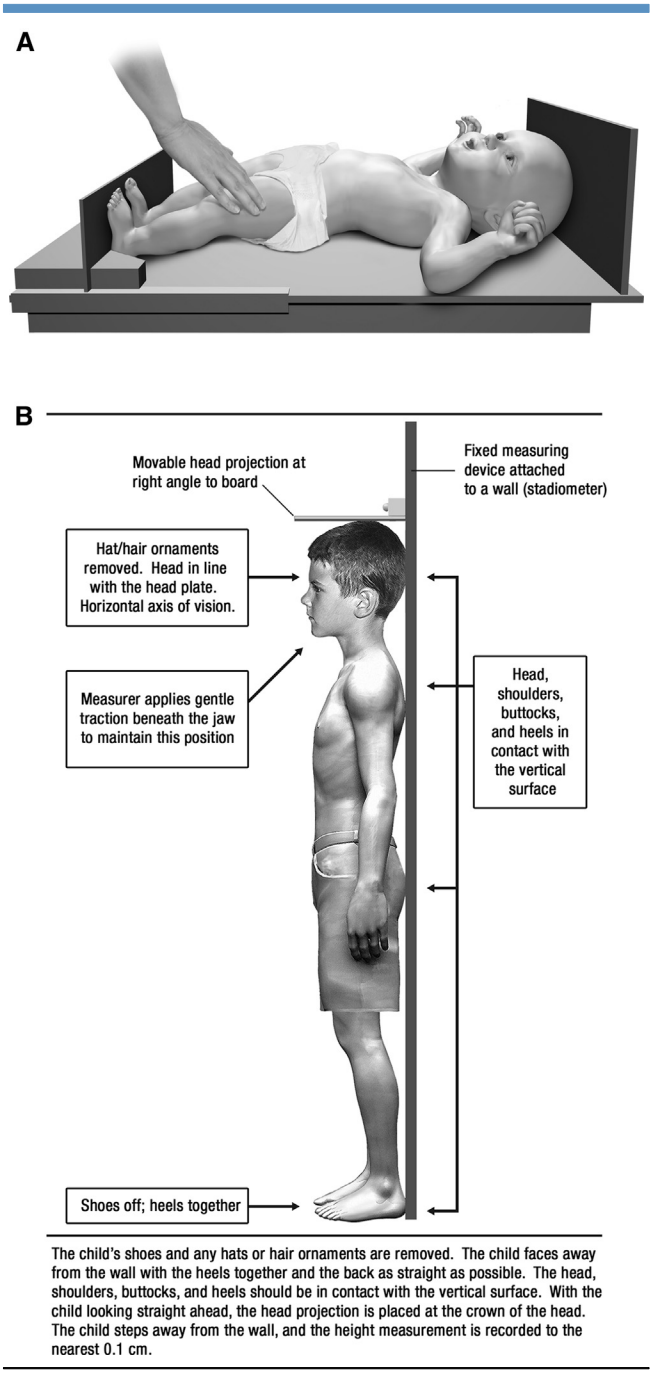

Figure 1. **A,** Infant length measurement technique. (Content and design by SPOON Foundation. Reproduced with permission from the Joint Council. Copyright © 2013, Joint Council. All rights reserved.) **B,** Height measurement technique.[10] (Adapted with permission from: Rogol AD. Diagnostic approach to short stature. In: Basow DS, editor. UpToDate. Waltham, MA: UpToDate; 2013. Copyright © 2013 UpToDate, Inc. For more information, visit www.uptodate.com.)

the nearest 0.1 cm[5] and measured twice, with results of the 2 measurements falling within a 4-mm range.[6] If the difference between the 2 values is >4 mm, then a third measurement should be obtained, with the average of the 2 closest values recorded. In a busy primary care office, a single carefully obtained measurement is usually considered sufficient if the value is consistent with the child's growth curve.

Accurate weight measurement depends on the accuracy and correct calibration of the scale. It is critical that the child be weighed without shoes and wearing only light clothing.

Techniques to evaluate growth have been standardized, including the routine use of growth charts as recommended by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC).[7-9] The 2006 WHO international growth standard charts represent growth standards for healthy children in optimal conditions and are now recommended as the preferred instruments for plotting growth in children aged <24 months. The CDC charts, used in the past for infants as well as children and currently recommended for children and adolescents aged 2-20 years, are reference charts documenting growth over time, as observed in subjects included in the data collection process.

The differences between these 2 chart types reflect their origins. Data used to create the WHO charts were obtained from the Multicenter Growth Reference Study (MGRS) conducted between 1997 and 2003 in 6 cities located in 6 different countries (Brazil, Ghana, India, Norway, Oman, and the US [California]). The MGRS was based on the hypothesis, later proven, that young children have similar growth potential independent of ethnicity and place of birth. When raised in a healthy environment and adequately nourished, children aged <24 months included in the MGRS reached comparable mean lengths in all 6 countries. Of note, children were excluded from the MGRS according to a number of criteria, including low socioeconomic status, breastfeeding for <12 months, maternal smoking during pregnancy or lactation, perinatal morbidities, and child health conditions known to affect growth. The CDC growth charts are based on data collected over time from 5 cross-sectional, nationally representative health examination surveys. For the growth charts for children aged <36 months, data were derived from the National Health and Nutrition Examination Surveys I, II, and III, conducted in the US from 1971 to 1994. From these surveys, the only exclusions were infants with very low birth weight. For the growth charts for children aged 2-20 years, data were derived from the National Health and Nutrition Examination Surveys I, II, and III as well as from the earlier National Health Examination Surveys II and III, conducted from 1963 to 1970.

Calculation of height velocity (HV) facilitates identification of a child's growth trajectory over time and evaluation of potential deviations from normal. While recognizing the potential for notable variation in HV among healthy children, the "rule of fives" can be used to estimate normal growth rates at various ages during childhood (**Figure 2**).[10] This convention suggests that growth may be rapid, at a rate of ~25 cm/year from birth to age 1 year, then moderate, at an average of 10 cm/year, from age 1 to 4 years.[10] In particular, children typically grow ~12 cm from age 1 to 2 years and 8 cm from age 2 to 3 years.[11] The rule of fives then suggests that growth further slows to ~5-

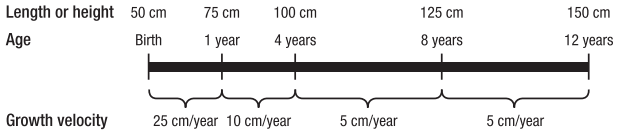

Figure 2. "Rule of fives" for estimating normal growth rates in children.[10] Normal length or height at various ages during childhood, and the growth rate between those timepoints, are approximated by multiples of 5, as shown above. Actual height and growth rate in a healthy child can vary substantially around these approximations. (Adapted with permission from Rogol AD. Diagnostic approach to short stature. In: Basow DS, editor. UpToDate. Waltham, MA: UpToDate; 2013. Copyright © 2013 UpToDate, Inc. For more information, visit www.uptodate.com.)

7 cm/year from age 4 to 8 years.[10] As illustrated in the infancy-childhood-puberty model developed by Karlberg et al,[12] HV is very high in the fetal period but decelerates rapidly in the 2-3 years after birth, with a slower but nearly constant growth rate in childhood that continues until puberty. A second peak in HV is observed at ~11.5 years of age for girls and ~13.5 years of age for boys in North America is associated with puberty and adolescent growth.[13] Growth hormone (GH) is produced in these 3 developmental stages and, along with other factors (eg, thyroid hormone, nutrition, genetic factors, general health status), is critical for growth beginning at age 6 months, whereas sex steroid hormones (ie, testosterone in boys and estrogens in girls) mostly contribute to growth during puberty.[11,12]

Longitudinally-based charts have been developed using data from cross-sectional studies to evaluate HV, taking into account the timing of puberty.[14] Current standards for determining HV are based on results from both cross-sectional studies and longitudinal growth studies and allow identification of children who develop growth abnormalities over time (**Figure 3**).[3] For optimal determination of HV, measurements should be obtained at 9- to 12-month intervals (after age 2 years), to minimize the effect of measurement errors and seasonal variations in growth.[3]

Multiple methods are available to generate estimates of adult height for children.[10] Target height (TH), an estimate of a child's genetic height potential, is most commonly determined by calculating the midparental height (MPH), using the following formulas[10,15]:

$$\text{TH (MPH) for girls}: \ ([\text{father's height cm} - 13\ \text{cm}] + \text{mother's height cm})/2 \ \text{(to determine average)}$$

$$\text{TH (MPH) for boys}: \ ([\text{mother's height cm} + 13\ \text{cm}] + \text{father's height cm})/2 \ \text{(to determine average)}.$$

For girls and boys, 8.5 cm on either side of the calculated TH equates to the 3rd to 97th percentiles for anticipated adult height.

A child tends to grow to be about as tall as his or her parents, but because men are generally taller than women, simply averaging the parents' heights will not suffice. Thus, for estimating a child's adult height, the MPH must be adjusted for the sex of the child.

Another method of predicting adult height takes into account the child's current height percentile,[16] but this method is not in widespread use given the wide range of predicted height.[17] In recent years, Web-based calculators have been devised to facilitate predictions of adult height according to available models. There are also more complicated methods for predicting adult height that are somewhat more accurate than using MPH but require additional testing and calculation[10]; for example, a radiograph of the left hand and wrist can be used to estimate bone age, which can serve as a surrogate for biological age and physical maturity.[18] This radiographic approach to evaluating skeletal maturation is based on the assumption that phalange and metacarpal development is representative of the development of vertebral and long bones, which serve as determinants of adult height. This approach is most useful in children with proportionate short stature. In children with skeletal dysplasia and other forms of disproportionate short stature, an extensive skeletal survey may be necessary for radiologic evaluation and accurate diagnosis.[18]

The concepts of weight-for-length and body mass index (BMI), as well as body composition (both lean body mass and fat mass), introduce additional measurements that determine the relative contributions to growth of different components (eg, weight vs length or weight vs height in BMI). Growth may be proportionate or disproportionate; in the latter case, different parts of the body develop in an unbalanced fashion. Measurements of head circumference, upper and lower body segments, and sitting height, as well as arm span, may provide important clinical information in addition to evidence of excessively short or tall stature. Head circumference is usually measured in infants and children up to age 3-4 years, with a flexible tape placed over the most prominent part of the back of the head, above the ears and the eyebrows (supraorbital ridges). Just as for length, head circumference should be measured to the nearest 0.1 cm.[5] Owing to the complexity of upper and lower body segment evaluation and the need for specific equipment, these measurements are often performed by specialists. Upper body:lower body is generally ~1.7 in neonates and decreases progressively to ~0.92 in white adults and ~0.88 in black adults.[3,19]

Monitoring Growth in Infants, Children, and Adolescents

"Normal" growth can be defined as a Gaussian phenomenon.[4] Values for continuous variables, such as height and weight, are distributed along a bell-shaped curve, also known in statistical terms as the normal distribution (a graphical representation of normal distribution can be found in an article by Rogol[4]). The total area under the curve includes

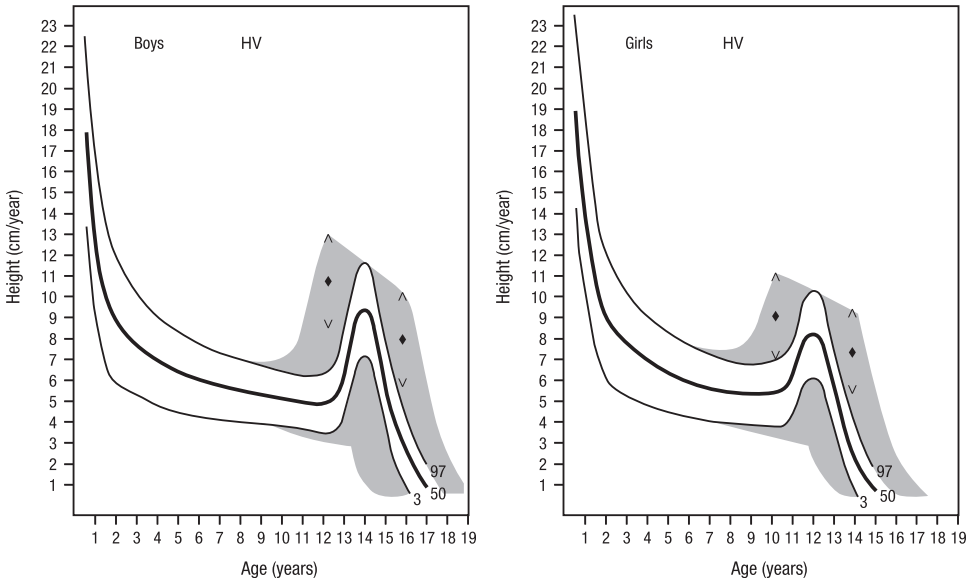

Figure 3. HV charts for boys and girls.[3] (Reproduced with permission from Cooke DW, Divall SA, Radovick S. Normal and aberrant growth. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors. Williams textbook of endocrinology. 12th ed. Philadelphia (PA): Saunders Elsevier; 2011. p. 935-1053. Copyright © 2011 Elsevier.)

100% of the analyzed population values, which are distributed to the left (eg, children with shorter stature compared with the mean) or to the right (eg, children with taller stature compared with the mean) of the mean value for that population, located at the center of the curve. The SDS, or *z*-score, is obtained by subtracting the mean value of the reference population from the observed value and dividing by the SD value of the reference population. For example, SDS for height is calculated as follows:

$$\text{Height SDS} = (\text{child's height} - \text{normal population mean for children of comparable age and sex}) / \text{SD of the height of children of comparable age and sex.}$$

The WHO Global Database on Child Growth and Malnutrition uses a range within 2 SD below and above the mean as the standard measure for identifying children with normal growth.[9] These limits correspond to the 2.3rd or 97.7th percentiles rather than to the 5th and 95th percentiles as in many older growth charts. A cutoff point of >2 SD below the mean is used to identify children with short stature (ie, low height for age), low weight for age, or low weight and low height for age. A cutoff point of >2 SD above the mean is usually used to identify children with tall stature.

With regard to body composition, various compartments can be identified, including a fat mass, a fat-free (lean) mass, and a bone mass.[20] The body composition measurement technique used may vary according to the clinical situation. Body composition may be affected by various pediatric diseases and conditions; one such example is the abnormal body composition characterized by obesity and reduced lean mass in children with Prader-Willi syndrome (PWS).[21]

Differentiating between Variants of Normal Growth and Pathological Short Stature

Growth failure may be detected during a routine well-child visit or on presentation with signs or symptoms of an acute or chronic illness, which may or may not be related to the child's current growth pattern. Clinical suspicion of growth impairment should prompt a review of the child's medical, family, and social histories, as well as a review of systems. Particular attention should be given to the series of issues outlined in Table I. A careful patient history may reveal abnormal growth in utero or after birth, as well as the presence of concomitant chronic diseases, such as gastrointestinal disturbances, renal disease, or hormonal deficiencies, that may serve to at least partly explain a change in growth pattern. A detailed family history may provide information on genetic TH (by providing data to calculate the MPH) and in some cases may suggest an increased risk of genetic abnormalities or certain specific genetic syndromes. When growth impairment becomes evident, maternal exposures and illnesses during pregnancy (eg, hypertension, preeclampsia) may assume renewed relevance and merit revisiting. It is also important to check for any symptoms of emotional deprivation or high levels of stress and/or anxiety.[22]

Subsequent steps for the general evaluation of growth failure in the pediatric setting include a physical examination (PE), careful examination of the patient's growth curve, and specific laboratory evaluations as required in each individual case.[1,3] As a component of the PE, the presence of dysmorphic features or disproportionate short stature may provide important diagnostic clues about the underlying

Table I. Patient history and review of systems in children presenting with growth impairment

	Question	Rationale
Past medical history	• Has the child had any past significant medical illnesses, hospitalizations, or surgeries? • How healthy was the pregnancy? Did the mother smoke, drink alcohol, or take any medication during the pregnancy? Did the mother have gestational diabetes? Was the child small, normal, or large for gestational age?	• Might suggest the possibility of a chronic disease that has not yet been identified but could interfere with growth (eg, a history of pneumonias and/or surgery in the neonatal period or meconium ileus could suggest the possibility of cystic fibrosis). • Excesses or constraints in the intrauterine environment can affect the child's size at birth and subsequent growth after birth.
Family history	• How tall are the child's mother and father, and how tall are the parents in the context of their own families? • When did the parents experience puberty (early vs late bloomer)? • Are there any diseases that run in the parents' families?	• May suggest the possibility of familial short stature or significant short stature for the genetic potential (target MPH). • May suggest the possibility of CDGP. • May suggest the possibility of a disease (eg, celiac disease) that has a genetic component and could interfere with growth.
Social history	• Do you have enough food and money to get through the month? • Has your child developed normally? How does your child do in school?	• Might suggest the possibility of food insecurity and malnutrition as a cause of poor growth. • Might suggest the possibility of a genetic or behavioral syndrome that could affect growth.
Review of systems	• Questions to evaluate all systems (eg, questions for the pulmonary and gastrointestinal systems) might include: Has your child had chronic cough, shortness of breath, diarrhea, and/or malabsorption?	• An as-yet unidentified chronic disease could interfere with growth (eg, cystic fibrosis, other gastrointestinal disease).

etiology of the growth aberration. The key issues to address during the PE are whether the patient has short stature in isolation or in conjunction with other physical or developmental abnormalities (which may suggest one of several syndromes), and whether the short stature is proportionate or disproportionate.[23] Proportionality may be evaluated using various measurements, namely arm span, sitting height to height and upper to lower segment ratios (with the former commonly measured in Europe and the latter in the US), and BMI, along with head circumference in children aged <3-4 years.[22-25] Examination of the proportionality of facial features is also important, given their association with certain growth-impairing genetic syndromes, including Turner syndrome (TS) and Noonan syndrome (NS).[22]

The usefulness of the information provided by the growth chart will depend in part on the availability of multiple accurate measurements of length or height to evaluate changes in HV (ie, trajectory) over time. For a child who is short, whether the HV is normal or diminished should be determined. All previous growth measurements should be carefully plotted on the most appropriate chart.[24] Special growth charts are available for children with certain conditions (eg, TS, NS). The use of these instruments may allow tailored diagnosis of growth defects specifically associated with well-known syndromes (**Figures 4-7**; available at www.jpeds.com).[26] Growth charts for boys and girls with NS are available online at http://noonansyndromefamily.files.wordpress.com/2011/08/noonangrowthcharts-m2-20-copy.jpg. and http://noonansyndromefamily.files.wordpress.com/2011/08/noonangrowthcharts-f2-20-copy.jpg.[27,28] Finally, the aforementioned weight-for-height charts can be applied to guide decisions regarding further evaluation and testing; being overweight for height may point toward certain types of endocrine disorders, whereas underweight for height is often suggestive of primary or secondary malnutrition.

Routine laboratory analysis, including a complete blood count with an erythrocyte sedimentation rate or C-reactive protein level and comprehensive metabolic panel, is a fundamental component of the early screening of many patients with growth failure. Abnormalities suggestive of anemia, chronic infection or inflammation, or organ dysfunction may point to the underlying etiology.[3,25,29] For example, anemia and/or infection may be presenting signs of various growth-impairing disorders, including celiac disease, cystic fibrosis, and Crohn's disease.[22] An exception to this rule of routine laboratory testing may be a child who is short but growing at a low-normal rate, is following the previous growth trajectory, and is entirely asymptomatic with an unremarkable review of systems and normal PE findings.[30] In a study, the likelihood of establishing a definite diagnosis in such a child by performing the "consensus" screening laboratory evaluation[24] was only ~1%.[30] This finding points to the need for evidence-based guidelines to determine appropriate laboratory screening of short children.

Thyroid function tests should be part of the early workup in many cases, given the known detrimental effects of hypothyroidism on brain development during infancy.[31] Measurement of thyroid hormone levels may uncover thyroid or pituitary insufficiency with isolated or multiple hormonal deficits, although, clinically, hormonal dysfunction is a less likely cause of growth impairment compared with chronic systemic illness and its therapy. Although an evaluation to diagnose rare conditions, such as Cushing syndrome, should be conducted only if there are clinical reasons to do so,[22] screening for celiac disease via anti-tissue transglutaminase or anti-endomysial antibody testing should be more routine.[22,24,32]

Depending on the clinical scenario, laboratory evaluations also may include measurement of insulin-like growth factor 1 (IGF-1) and IGF-1 binding protein 3, with the latter having applicability for diagnosing GH deficiency (GHD), especially in children aged <3 years.[24] Decisions regarding GH testing may be guided by IGF-1 levels, HV, or a combination of history and PE findings, with broad (albeit not universal) expert

consensus that GH testing should not be pursued in children who are short but have a normal HV, no delay in bone age, and an IGF-1 level above or near the mean for age.[22,24] Conversely, GH testing would be indicated in patients with a low IGF-1 value for age or, alternatively, within the lower normal range when accompanied by other clinical factors suggestive of GHD.[22] Because GH is secreted in an intermittent pulsatile manner, there is little value in a single determination; however, if GHD continues to appear in the differential diagnosis, stimulation testing with GH secretagogues may be performed by a pediatric endocrinologist. Overall, there is substantial potential for false-positive or false-negative results with this type of testing, and interpretation of findings generally remains within the realm of the pediatric endocrinologist.[4]

Radiologic examination may aid diagnosis by revealing delayed (or advanced) bone age or skeletal defects characteristic of a specific syndrome, such as a skeletal dysplasia or a genetic syndrome such as TS or short stature homeobox (SHOX) deficiency. Hand-wrist radiographs obtained to determine bone age and skeletal surveys (performed only in cases of suspected skeletal dysplasia) should be subject to expert review.[22,24] GHD is highly unlikely in patients without evidence of bone age delay.[22]

Clinicians are also faced with questions regarding the appropriate use of magnetic resonance imaging of the brain and genetic testing. Based on the consensus derived at an international meeting on idiopathic short stature (ISS), pituitary magnetic resonance imaging is warranted in patients with suspected GHD (owing to the potential for underlying intracranial abnormalities), but not on a routine basis for short children, assuming no evidence of intracranial involvement or midline defect.[22] Genetic tests can contribute to a diagnosis in children with short stature associated with the aforementioned genetic syndromes; medical history and PE findings are critical for the decision-making process regarding genetic testing.[22]

Variants of Normal Growth

A number of conditions represent variants of normal growth rather than abnormal states, including familial short stature (**Table II**), constitutional delay of growth and puberty (CDGP) (**Table III**), small for gestational age (SGA) with catch-up growth (**Table IV** and **Figure 8**; **Figure 8** available at www.jpeds.com), and early puberty (not the pathological condition precocious puberty) with accelerated growth, maturation, and early epiphyseal fusion.[3,33-37] It is important to identify and differentiate these conditions from abnormal patterns of growth to appropriately manage these infants, children, and adolescents and advise their parents and family members. In the vast majority of cases, these variants of normal growth are identified and managed by general pediatricians in their clinical practice and do not require specialist referral.

Familial (or genetic) short stature represents a normal variant of growth in children, based on polygenic inheritance of growth-associated genes.[3] Estimates of TH according to MPH and evaluation of other growth variables help distinguish these children from those with pathological growth failure. In children with familial short stature, height is at the lower end of the distribution curve and may fall below the 3rd percentile. Parents are often below the 10th percentile in height. Measuring the parents' height is important,

Table II. Familial short stature[3,34]

Growth-related history and patient PE	• Children with familial short stature have a height below the 2.3rd percentile. • Normal HV • Bone age concordant with chronological age • Time of puberty onset comparable to peers • Parent(s) of short stature, usually below 10th percentile
Imaging and other evaluations	• Estimate of TH based on MPH • Determination of bone age may be helpful to rule out CDGP. • Other potential evaluations to exclude unrelated conditions and diseases associated with short stature and growth failure generally are not indicated.
Laboratory evaluation	• If performed, general laboratory evaluation and GH and IGF-1 levels are within normal ranges.
Rationale for treatment and treatment modalities	• No treatment needed. • Growth monitoring during childhood and adolescence • Education and counseling of patient and family members

Table III. CDGP[3,33,34,37]

Growth-related history and patient PE	• Normal size at birth • Reduced HV in the first 3-5 y of life • Growth and stature concordant with bone age but not with chronological age • Good health status and normal HV in childhood, with perhaps some slowing just before the delayed growth spurt • Delayed but normal puberty • Growth to normal height during delayed puberty • Observed in families with short or tall family members • Family history may reveal individuals with CDGP.
Imaging and other evaluations	• Determination of bone age • Other potential evaluations to exclude unrelated conditions and diseases associated with short stature and growth failure • Important to differentiate CDGP from pathological causes of short stature or growth failure
Laboratory evaluation	• If performed, general laboratory tests and GH and IGF-1 levels are usually within normal ranges. • Determination of sex hormone status in adolescence is sometimes helpful.
Rationale for treatment and treatment modalities	• No specific medical or surgical treatment needed in most cases. • Growth monitoring during childhood and adolescence • Education and counseling of patient and family members • Short course of testosterone in some boys or estrogen in some girls

Table IV. SGA[35,36]

Growth-related history and patient PE	• Children born SGA have lower than expected weight and/or length for age and sex (eg, at least 2 SD below the mean for gestational age, equivalent to being at or below the 2.3rd percentile). • Infants may be SGA with low birth weight, SGA with low birth length, or SGA with low birth weight and length. • SGA should be differentiated from IUGR due to a specific, identified cause. • Approximately 10%-15% of SGA infants do not experience catch-up growth by age 2 y and may have persistent short stature in childhood.
Imaging and other evaluations	• Ultrasonography to document gestational age • Length and weight evaluations at birth; height, weight, and BMI evaluations in childhood • Specialist referrals as needed (eg, children with SGA and no catch-up growth by age 2 y)
Laboratory evaluation	• If performed, general laboratory tests and GH and IGF-1 levels are usually normal.
Rationale for treatment of those children who fail to catch up to the lower growth percentiles by age 2 y and treatment modalities	• Primary objective of treatment is to accelerate linear growth in SGA children with no catch-up growth by age 2 y. • rhGH therapy (GHT) increases HV and childhood height in SGA patients who fail to catch up to the lower growth percentiles. • Early treatment may favor rapid catch-up growth early in childhood. • Treatment with rhGH should be continuous rather than intermittent to achieve the greatest benefit. • Factors associated with response to GHT include age and height SDS at the start of treatment, MPH, rhGH dose, and IGF-1 level during GHT.

GHT, GH therapy; *rhGH*, recombinant human GH.

Table V. Achondroplasia[39,40]

Growth-related history and patient PE	• Disproportionate short stature (birth length may be within the normal range) • Rhizomelic (proximal) limb shortening • Other characteristics include midfacial hypoplasia with relative macrocephaly and frontal bossing, lumbar lordosis, and "trident" hands that are short and broad with increased space between the middle 3 fingers so as to give a fork-like appearance. • Children generally do well, although delayed motor development, otitis media, and lower leg bowing are common; less frequent but serious complications (5%-10% of cases) include hydrocephalus, craniocervical junction compression, upper airway obstruction, and thoracolumbar kyphosis. • Average adult height is ~48 inches (122 cm) in both men and women. • Achondroplasia may affect between 1:26 000 and 1:40 000 live births.
Imaging and other evaluations	• Radiographic evaluation only for diagnostic purposes or for suspected complications • Assessment of neurologic history and examination, neuroimaging (computed tomography or magnetic resonance imaging), and polysomnography to evaluate brain stem compression and craniocervical junction risks (which might not exhibit clinically detectable physical features or symptoms) • Routine length and weight measurements, with measurement of head circumference at each visit during the first year and ongoing assessment thereafter (owing to the risk of hydrocephalus); review of weight control and diet over time • Ear and hearing examinations (because of an increased risk of otitis media with effusion), with formal audiometric assessment at age 9-12 months and annual hearing screening through late childhood • Specialist referrals as needed
Laboratory evaluation	• No specific routine laboratory testing
Special testing (if applicable)	• Genetic testing for *FGFR3* mutations is available.
Rationale for treatment and treatment modalities	• Extended limb-lengthening surgery may be considered but is associated with a number of shortcomings/risks (not commonly used in North America).

because verbal reports of height are often erroneous, most typically overestimating the measured height. In children with familial short stature, HV is normal, onset of puberty is comparable with that of peers, and bone age is in agreement with chronological age. Adult height in these children is usually within the expected range based on family history (**Table II**).[3]

Children with CDGP experience puberty later than their peers.[3] There is often a history of similar "late blooming" in one or both parents and other family members. Of normal size at birth, children with CDGP have a low HV in the first 3-5 years of life but normal HV in the subsequent childhood years. Their height may be at or slightly below the 5th percentile until they enter puberty and experience the associated growth spurt, which in most cases results in a normal TH. If the onset of puberty is particularly late, the growth rate may decline to <4.5-5 cm/year. Adolescents with CDGP usually require monitoring, but not treatment. Some selected boys may benefit from referral to a pediatric endocrinologist for consideration of androgen therapy, and some selected girls likewise may benefit from consideration of estrogen therapy (**Table III**).[3,33,34,37]

Intrauterine growth restriction (IUGR), which may reflect maternal and/or fetal issues, is commonly defined as a fetal weight below the 10th percentile for gestational age (as determined by ultrasound) and may result in an SGA fetus or infant. Historically, the terms IUGR and SGA have been used interchangeably; however, increasingly the consensus convention is to use IUGR only to describe infants with confirmed prenatal growth impairment with an established underlying cause.[3] Infants born with a body weight and/or length at least 2 SD below the mean for gestational age and sex, equivalent to the 2.3rd percentile, are considered SGA.[35,36,38] Sometimes infants with birth weight and/or length below the 5th or 10th percentile for gestational age and sex are considered SGA, but we prefer a

Table VI. TS[41,44]

Growth-related history and patient PE	• Characterized by short stature (average adult height ~20 cm shorter than TH), in addition to potentially serious cardiovascular abnormalities. • Disproportionate growth (stocky figure) • Skeletal abnormalities (eg, scoliosis, kyphosis, hip dislocation) are sometimes present; short 4th metacarpal bone is common. • Short neck, neck webbing, *cubitus valgus, genu valgum* • May affect between ~1/2000 and 1/5000 females at birth
Imaging and other evaluations	• Radiography to evaluate potential skeletal abnormalities • Other evaluations for TS-associated morbidities • Specialist referrals as needed; cardiology evaluation is indicated due to the increased incidence of coarctation of the aorta or structural heart defects
Laboratory evaluation	• Standard hematologic screening tests (eg, hemoglobin, white blood cell count) • Evaluation of IGF-1 status during GHT • Renal function (creatinine and serum urea nitrogen) • Blood glucose, lipid profile, liver enzymes • TSH, total or free T4, thyroid antibodies • Anti-tissue transglutaminase antibodies
Special testing (if applicable)	• Genetic testing: karyotype analysis to identify a potential 45,X genotype with partial or complete loss of the second chromosome X, or related defects (eg, ring X chromosome)
Rationale for treatment and treatment modalities	• Treatment with rhGH (GHT) is standard of care for patients with TS and short stature. • GHT increases adult height with no detrimental effects on the cardiovascular system. • Early initiation of GHT is associated with greater adult stature. • Thyroid hormone (autoimmune thyroiditis) • Estrogen therapy (primary hypogonadism) • Gluten-free diet (celiac disease)

T4, thyroxine; *TSH*, thyroid-stimulating hormone.

Table VII. PWS[21,45,47,84]

Growth-related history and patient PE	• Hypotonia is a typical feature of infants with PWS, including diminished fetal movements. • Developmental delay is common in PWS. • Short stature and/or growth failure are associated with reduced HV and accelerated weight gain. • Evidence of reduced muscle mass and increased fat mass • Reported birth incidence of PWS is ~1/30 000.
Imaging and other evaluations	• Radiography to evaluate potential scoliosis • Other evaluations for PWS-associated morbidities • Specialist referrals as needed; evaluation for sleep apnea is important, particularly in children who will be treated with rhGH
Laboratory evaluation	• Evaluation of GH and IGF-1 status • Oral glucose tolerance test, particularly in the presence of obesity • TSH, free T4, and free T3 measurements before and during GH treatment
Special testing (if applicable)	• Chromosomal microarray or fluorescence in situ hybridization analysis to detect chromosome 15q11-q13 deletions • A negative karyotype or fluorescence in situ hybridization analysis does not rule out PWS. • DNA methylation analysis should be able to detect both microdeletions and uniparental disomy. • Further genetic testing may be done to identify an imprinting defect in specific cases if the other tests are unrevealing.
Rationale for treatment and treatment modalities	• Aim of treatment with rhGH (GHT) in PWS is to improve body composition and increase growth in childhood and adult height. • GHT significantly increases height, HV, and lean mass (improved body composition). • Early initiation of treatment with rhGH may provide greater benefit.

T3, triiodothyronine.

stricter definition. Although the majority of infants born SGA achieve normal length with "catch-up growth" by age 2 years, approximately 10%-15% do not do so and have persistent short stature in childhood. Catch-up growth may be more delayed, to 4 years, in preterm infants born SGA.[35] The diagnosis of SGA may be aided by ultrasonography-based determination of gestational age, requiring at least 2 measurements, along with an accurate measurement of birth length (**Table IV**).[35,36]

Common Pathological Growth Patterns

Numerous conditions can be associated with pathological growth patterns, which vary according to the causes and manifestations of the associated syndromes or diseases (**Figures 4-7**). First, a number of well-characterized genetic syndromes often present with growth defects and short stature, including chondrodystrophy and achondroplasia (**Table V** and **Figure 7**)[39,40] and various syndromes, including TS (**Table VI**),[26,41-44] PWS (**Table VII**),[21,45-48] NS (**Table VIII**),[49-51] and short stature due to SHOX deficiency (**Table IX**).[52] The distinctive clinical and radiographic characteristics of achondroplasia typically lead to its early diagnosis during the prenatal or newborn periods by ultrasound detection of long bone foreshortening or newborn evaluation; however, historically, ~20% of diagnoses occurred later in infancy.[39] In cases in which genetic conditions such as those mentioned previously are not diagnosed before or shortly after birth, evidence of growth impairment may coincide with the emergence of classic signs and symptoms during infancy or in later years; for example, hypotonia is common in infants with PWS, typically associated with a poor sucking reflex.[21] Hypotonia generally improves in the postinfancy period, and weight gain likely accelerates, resulting in central obesity, and global developmental delays may become increasingly apparent over time. Although the combination of symptoms is clinically relevant in PWS, unexplained short stature alone may be the only sign of TS in girls and may be the sole criterion for performing a karyotype analysis to confirm or rule out this disorder.[3,25] Distinctive facial features or right-sided heart disease observed in infancy frequently lead to a diagnosis of NS,[50] but many children with short stature due to SHOX deficiency display no characteristic signs other than short stature.[52]

Short stature also may be a manifestation of chronic systemic diseases affecting children, including chronic kidney disease (**Table X**),[53-57] Crohn's disease (**Table XI**),[58] juvenile idiopathic arthritis (**Table XII**),[59,60] nutritional deficits, gluten enteropathy, cystic fibrosis, and hematologic or solid malignancies and the associated antineoplastic

Table VIII. NS[49,50,85]

Growth-related history and patient PE	• Birth weight and length are usually normal. • Manifestations of NS may vary based on the underlying genetic defect, but right-sided cardiac findings are common. • Developmental delays, growth failure, and short stature are frequently observed in NS (~50%-70% of cases). • Scoliosis and other spinal abnormalities are present in up to 10%-15% of children with NS. • NS may affect between ~1/1000 and 1/2500 live births.
Imaging and other evaluations	• Other evaluations for NS-associated morbidities • Specialist referrals as needed
Laboratory evaluation	• Evaluation of GH and IGF-1 status • TSH, free T4, and free T3 measurements
Special testing (if applicable)	• Most frequent genetic defect in NS identified by *PTPN11* gene sequencing. • *KRAS*, *SHOC2*, *RAF1*, and *SOS1* gene sequencing also may help identify the genetic defect associated with a specific case of NS. • Genetic testing confirms diagnosis. • Negative genetic testing results do not exclude a clinical diagnosis of NS.
Rationale for treatment and treatment modalities	• Treatment with rhGH (GHT) increases adult height. • Effectiveness of GHT in NS is increased by early initiation and longer duration of treatment.

KRAS, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; *PTPN11*, tyrosine-protein phosphatase nonreceptor type 11; *RAF1*, v-raf-1 murine leukemia viral oncogene homolog 1; *SHOC2*, soc-2 suppressor of clear homolog (*Caenorhabditis elegans*); *SOS1*, son of sevenless homolog 1 (*Drosophila*).

treatment regimens.[3] Long-term treatment with corticosteroids (eg, immunosuppressive glucocorticoids) in children with chronic kidney disease, particularly at higher doses, may lead to altered bone homeostasis and growth failure.

Table IX. Short stature due to SHOX deficiency[52]

Growth-related history and patient PE	• Birth length is usually only mildly reduced in children with SHOX deficiency. • Growth failure is usually noted in early childhood. • SHOX deficiency is associated with short stature and a variable somatic phenotype. • More severe and more frequently symptomatic in girls. • Disproportion of limbs with reductions in arm span and leg length (extremity to trunk ratio <−1 SDS) • Madelung deformity of the forearm (wrist) with spontaneous subluxation of the distal ulna • Other skeletal defects
Imaging and other evaluations	• Radiologic evaluations of forearm searching for 3 signs: triangularization, pyramidalization, and lucency of distal radius • Specialist referrals as needed
Laboratory evaluation	• None
Special testing (if applicable)	• Genetic testing for *SHOX* abnormalities • *SHOX (X)* deletions more frequent than *SHOX (Y)* deletions • Patients with TS may have defects or loss of 1 *SHOX* allele.
Rationale for treatment and treatment modalities	• Treatment with rhGH (GHT) in children with SHOX deficiency increases HV and height SDS. • Extent of benefit with GHT in SHOX deficiency syndrome is comparable to that seen in TS.

Table X. Chronic kidney disease[54-56]

Growth-related history and patient PE	• Growth failure is often present in children with chronic kidney disease. • Related to nutritional, hormonal, and/or metabolic defects, as well as to long-term corticosteroid therapy. • Greater height deficits are seen in children affected by chronic kidney disease at a younger age. • Growth defects often persist during/after dialysis and after kidney transplantation.
Imaging and other evaluations	• Specialist referrals as needed
Laboratory evaluation	• Standard biochemical and hematologic tests • Monitoring of renal function
Rationale for treatment and treatment modalities	• Children with chronic kidney disease and short stature who do not grow normally despite appropriate nutritional interventions and other disease-related treatments may benefit from GHT with sustained catch-up growth. • Initiation of GHT at a young age and continuous therapy is associated with a greater likelihood of achieving the adult TH. • Negative predictors of response to GHT in chronic kidney disease include durations of dialysis and pubertal delay.

Glucocorticoids affect various targets in different systems, leading to reduced estrogen levels, inhibited IGF-1 production, and resistance to IGF-1. All of these negative effects result in inhibited chondrocyte proliferation, decreased matrix synthesis, and, ultimately, reduced linear growth.[61]

Defects in endocrine function with abnormal production of GH and/or other hormones may lead to height deficits, as observed in children affected by GHD (**Table XIII**),[4,62-65] hypopituitarism,[3] hypothyroidism (**Table XIV**),[66-68] and Cushing syndrome (**Table XV**).[69-71]

Short stature also may be documented in children in whom no related cause can be identified after a careful search; such cases are included in the category of ISS (**Table**

Table XI. Crohn's disease[58]

Growth-related history and patient PE	• Up to ~50% of children and adolescents with Crohn's disease present with short stature and growth failure. • As many as 90% may be underweight. • Often associated with late puberty.
Imaging and other evaluations	• Endoscopic and radiologic evaluation/ confirmation of Crohn's disease • Specialist referrals as needed
Laboratory evaluation	• Markers of inflammation and nutritional status
Rationale for treatment and treatment modalities	• Enteral nutrition and interventions (including intestinal surgery) that induce remission have a positive impact on catch-up growth of affected children. • Nutritional interventions are most effective in small-bowel disease and in prepubertal children (limited window of opportunity). • Monoclonal antibodies to destructive cytokines may lead to significant diminution of disease activity.

Table XII. Juvenile idiopathic arthritis[59,60]

Growth-related history and patient PE	• Approximately 10%-40% of children with juvenile idiopathic arthritis have short stature due to long-term inflammation, stiffening, and deformation of affected joints. • Delayed puberty • Short stature is generally related to reduced growth in lower extremities. • Clinical course is highly variable among patients. • Incidence is 6-19/100 000.
Imaging and other evaluations	• Regular monitoring of growth and physical development
Laboratory evaluation	• None
Special testing (if applicable)	• None
Rationale for treatment and treatment modalities	• Treatment goals include inducing remission and reducing dose and duration of corticosteroid treatment; timely initiation of treatment can preserve growth potential. • Inflammation and clinical symptoms can be treated using corticosteroids (which may limit growth, however), methotrexate, immunosuppressant drugs, or biological agents.

XVI).[22,24,63,65,72,73] Although ISS is a diagnosis of exclusion, consensus is lacking as to which systemic diseases should be excluded before establishing this diagnosis.[22] Children with ISS may be categorized as having familial short stature (as discussed previously) or nonfamilial short stature, in which the child is short not only for the population range, but also for the familial target range. Further subcategorization is based on the timing of pubertal onset.

Table XIII. GHD[62-65]

Growth-related history and patient PE	• Infants and children with GHD have growth failure. • Short stature and growth failure may be the only clinical features present. • GHD may affect ~1/3500 children.
Imaging and other evaluations	• Diagnosis is based on clinical, auxologic, and biochemical parameters. • Radiologic evaluation of bone age • Central nervous system magnetic resonance imaging or computed tomography scan to evaluate the hypothalamic-pituitary region and to exclude other conditions • Evaluation and management by a pediatric endocrinologist
Laboratory evaluation	• Measurements of GH, IGF-1, and IGF-1–binding protein levels • Determination of peak GH levels after stimulation test
Special testing (if applicable)	• Family history and genetic analyses (eg, search for *PROP1* and *POU1F1* mutations)
Rationale for treatment and treatment modalities	• Replacement therapy with rhGH (GHT) • Predictors of greater benefit with GHT in GHD include early initiation of treatment, higher rhGH dose, and IGF-1–guided dosing. • GHT should be started as soon as GHD is diagnosed.

PROP1, homeobox protein prophet of Pit-1; *POU1F1*, POU class 1 homeobox 1.

Table XIV. Hypothyroidism[66-68]

Growth-related history and patient PE	• Hypothyroidism may be related to multiple causes, including environmental conditions (eg, deficient iodine intake), trauma or tumors in the hypopituitary region, and congenital defects. • Depending on cause, hypothyroidism may occur in children of any age, from neonates to adolescents. • Depending on severity and duration of the defect in thyroid hormone production, hypothyroidism may be associated with growth deficit and short stature in affected children. • Congenital hypothyroidism is reported in ~1/3000 newborns from the routine screening programs.
Imaging and other evaluations	• Thyroid ultrasonography and scintigraphy when indicated • Mother's medical history and list of medications • Other evaluations for hypothyroidism-associated morbidities • Specialist referrals as needed
Laboratory evaluation	• Key to diagnosis of hypothyroidism are measurements of TSH and free T4 levels, compared with age-matched unaffected children.
Special testing (if applicable)	• Measurements of autoimmune anti-thyroid antibodies (in the infant and the mother) if the mother has a history of autoimmune thyroiditis (Graves disease). • Genetic analysis may allow identification of mutations affecting biosynthesis of thyroid hormone(s) in affected children.
Rationale for treatment and treatment modalities	• Diagnosis should be made as early as possible to initiate appropriate replacement therapy with thyroid hormones (levothyroxine). • Target of treatment is to normalize TSH concentrations, and maintain T4 and free T4 within upper half of reference range. • Specific treatment allows catch-up growth and prevention of other serious manifestations (eg, mental retardation). • Children with congenital hypothyroidism treated in the first few weeks of life often achieve near-normal intellectual and growth outcomes.

Further Evaluation and Referral to a Pediatric Subspecialist

Although genetic syndromes associated with pathological stature are not very common (see the incidence data in the Tables I-XVI), studies suggest that there are often significant delays in diagnosis.[74] For example, in a Danish series of 746 female patients (children and adults) with a karyotype compatible with a diagnosis of TS, the median age at diagnosis of TS was 15 years (range, 0-86 years), rather than at a younger age that would potentially have allowed for earlier therapeutic interventions.[42]

Pediatricians, primary care physicians, physician assistants, and nurse practitioners have critical roles in the early identification of children with pathological short stature and prompt referral of these children to pediatric subspecialists

Table XV. Cushing syndrome[69-71]

Growth-related history and patient PE	• Up to 65% of childhood cases of Cushing syndrome have an adrenal origin. • Growth arrest is a characteristic feature of Cushing syndrome in children. • Typically, affected children have short stature but high BMI (above the mean for age and sex). • Growth failure may be one of the first manifestations of Cushing syndrome in children. • The pattern of obesity associated with Cushing syndrome is generalized.
Imaging and other evaluations	• Imaging studies to identify cause of Cushing syndrome • Other evaluations for Cushing-associated morbidities • Specialist referrals as needed
Laboratory evaluation	• Measurement of circadian cortisol levels • Levels of urinary free cortisol • High-dose dexamethasone suppression test
Rationale for treatment and treatment modalities	• Specific treatment of adrenal pathology is of high priority in children with Cushing syndrome. • Catch-up growth is observed in the majority of treated patients.

Table XVI. ISS[22,24,65-73]

Growth-related history and patient PE	• Short stature may be the sole clinical feature in a child with ISS. • Diagnosis is usually based on a height >2 SD below the mean, in the absence of evidence of systemic, endocrine, nutritional, or genetic abnormalities (diagnosis by exclusion). • Between 60% and 80% of children with height ≥2 SD below the mean may have ISS.
Imaging and other evaluations	• Clinical, auxologic, and biochemical tests are used to diagnose ISS vs other conditions. • Radiologic evaluation of bone age • Other investigations to exclude other conditions • Specialist referrals as needed
Laboratory evaluation	• Routine biochemical and hematologic tests • Measurements of IGF-1 • Determination of peak GH levels after stimulation test to differentiate from GHD (>10 μg/L) or a downward-adjusted reference standard • TSH and total or free T4 • In a child without symptoms or signs on PE, watchful waiting without further testing (except for perhaps a bone age film) may be appropriate.
Special testing (if applicable)	• Karyotype analysis is recommended for all girls with unexplained short stature and for boys with concomitant genital abnormalities. • Chromosomal microarray testing may be helpful.
Rationale for treatment and treatment modalities	• Treatment with rhGH (GHT) may be appropriate in children with ISS and ≥2.25 SD below the mean height for age and sex (≤1.2nd percentile). • Responses to GHT may be more variable in children with ISS compared with children with GHD. • IGF-1–based dosing may help optimize efficacy of treatment with rhGH. • Safety profile of GHT in ISS is comparable to that observed in other indications.

for diagnosis and selection of case-tailored therapeutic interventions.[74-78] Growth pattern monitoring may lead to earlier diagnosis of underlying pathological conditions, including cystic fibrosis.[79] In clear-cut cases of growth failure, referrals are driven mostly by clinical criteria, according to published guidelines. Public health–related attempts to promote the early diagnosis and treatment of children with short stature have led to guidelines for referral that have been shown to lead to varying numbers of referrals, with excessive numbers in some cases and insensitivity for detecting certain growth abnormalities (such as those associated with TS) in others.[80] In 2008, researchers in The Netherlands published evidence-based guidelines for population-based growth monitoring specifically in children aged ≥3 years driven by distance from TH (**Figure 9**; available at www.jpeds.com)[32]; however, this method is not appropriately predictive for use in children aged <3 years.[25] Instead, weight trajectory may have increased utility over length trajectory in identifying infants with diminished growth from cystic fibrosis or celiac disease.[81]

In children with the slowest normal growth rates, including many with ISS, other factors, such as family concerns, health care professionals' attitudes, and patient demographic characteristics, may significantly influence the decision to refer a child with short stature to a pediatric subspecialist.[74,82,83] One study found that the number and types of referrals of new patients for short stature were not equally balanced between boys and girls; for example, a greater proportion of the referred boys were of normal height (38% vs 20%; $P < .01$).[82] Compared with the general population and with their MPHs, the height deficits were more pronounced in girls, particularly after age 9 years, and more girls had an organic disease (41% vs 15%). Such sex-related differences in referral of girls and boys with short stature potentially could lead to underdiagnosis and undertreatment of girls with a myriad of conditions, including TS and GHD.[78,82,83] These study results, which may reflect general perceptions of height- and sex-related expectations during childhood development, highlight the need to maintain high standards in growth monitoring and growth failure/short stature referrals for both girls and boys, to avoid underdiagnosis of potentially manageable conditions. Pediatricians and other health care professionals also should consider family members' concerns, as well as patients' preferences, to provide the needed education, support, and best available care for each child.

Discussion

Short stature in infants, children, and adolescents may be due to variations in normal growth or to pathologic states. Accurate assessment and monitoring of growth in children is of critical importance for early identification of defects

associated with treatable conditions versus growth variations associated with normal conditions.[3] Key parameters related to growth should be monitored, including length or height according to age, weight, BMI, and HV compared with the mean of the reference populations for boys and girls. In selected children, additional testing will be helpful, such as complete blood count, comprehensive metabolic panel, bone age, GH, IGF-1, and TSH/T4 status.[3,63]

Careful growth monitoring in the pediatric office may allow identification of children with familial (or genetic) short stature, CDGP, or SGA with catch-up growth, which are normal variants of growth and usually do not require specific treatment or referral to a pediatric endocrinologist. The differential diagnosis of children with a pathologic growth impairment may be complex because a substantial number of syndromes and diseases are associated with short stature and growth failure. In the case of children with evidence of growth failure and pathologic short stature, referrals to pediatric endocrinologists and other specialists, as needed, will help ensure accurate identification of the underlying cause(s) and selection of treatment tailored for each specific child. Appropriate diagnosis and management of pathologic growth states in other diseases, such as hypothyroidism, Cushing syndrome, Crohn's disease, gluten enteropathy, cystic fibrosis, and malignancies, may also contribute to substantial improvements in overall clinical outcomes for affected children. Treatment with rhGH can help achieve target adult height in selected children with short stature due to SGA without catch-up growth, GHD, hypopituitarism, SHOX deficiency, ISS or CKD, and complex genetic syndromes such as TS, NS, and PWS.[74,76-78] Early diagnosis, referral, and treatment improve the likelihood of a successful outcome. ■

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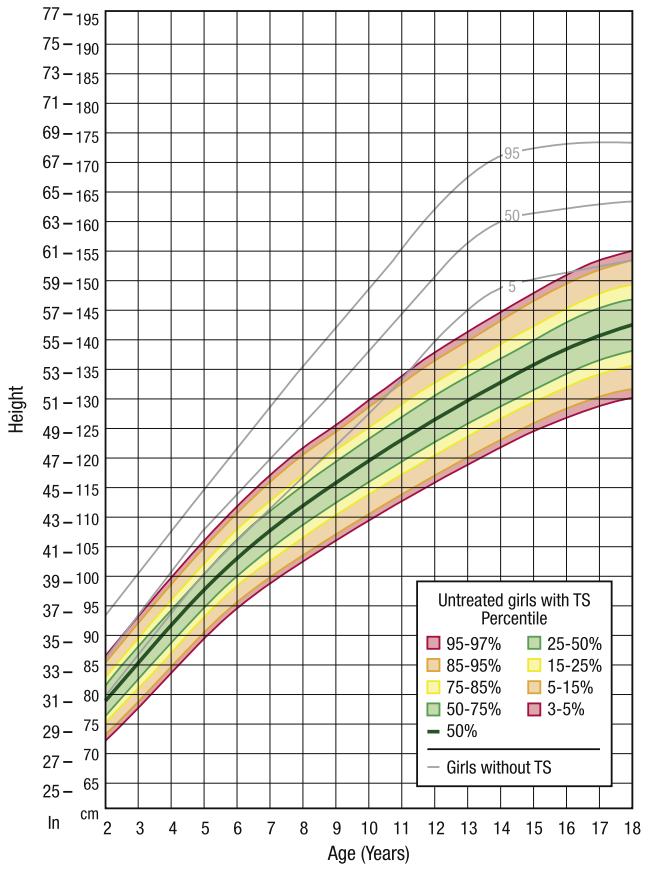

Figure 4. TS growth chart.[28] (Adapted with permission from https://mygrowthcharts.com. Copyright © 2004-2013 Medda LLC.)

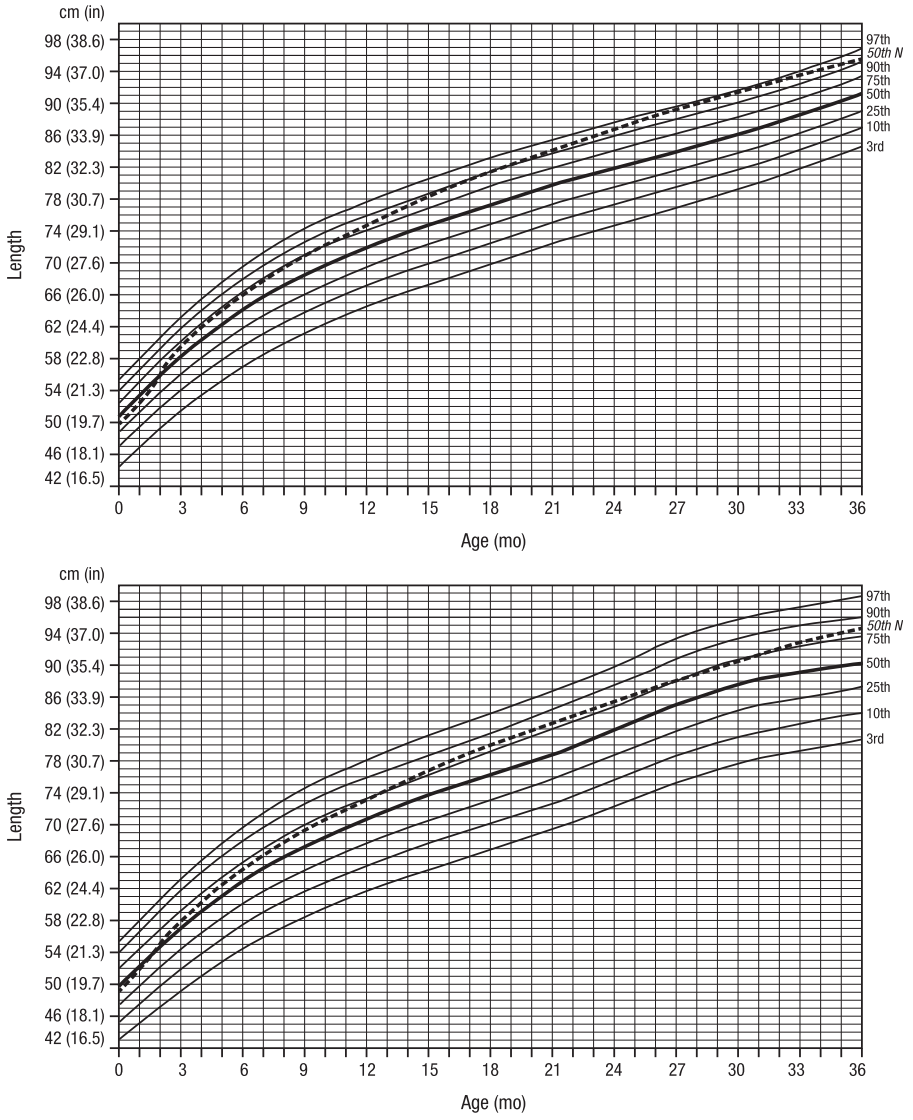

Figure 5. Standardized length charts for infants with PWS (aged 0-36 months).[86] *Dotted line* indicates normative 50th percentile. (Reproduced with permission from Butler MG, Sturich J, Lee J, Myers SE, Whitman BY, Gold JA, et al. Growth standards of infants with Prader-Willi syndrome. Pediatrics 2011; 127:687-95. Copyright © 2011 American Academy of Pediatrics.)

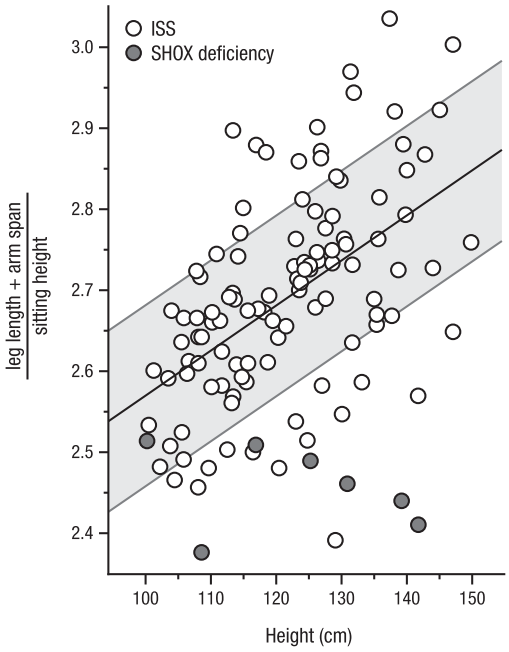

Figure 6. Extremity–trunk disproportions in short stature due to SHOX deficiency.[50] (Reproduced with permission from Binder G. Short stature due to SHOX deficiency: genotype, phenotype, and therapy. Horm Res Paediatr 2011; 75:81-9. Copyright © 2011 Karger Publishers, Basel, Switzerland.)

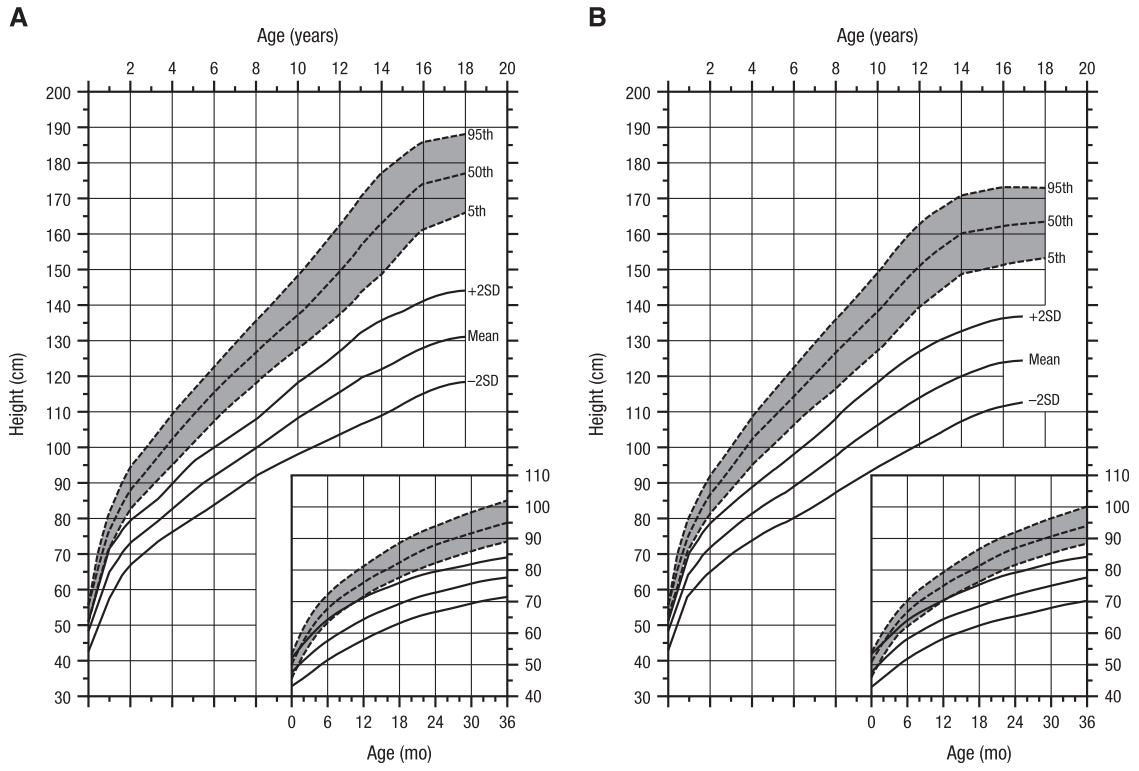

Figure 7. Achondroplasia growth chart for **A,** boys and **B,** girls.[39,87] (Reproduced with permission from Trotter TL, Hall JG. Health supervision for children with achondroplasia. Pediatrics 2005; 116:771-83. Copyright © 2011 American Academy of Pediatrics.)

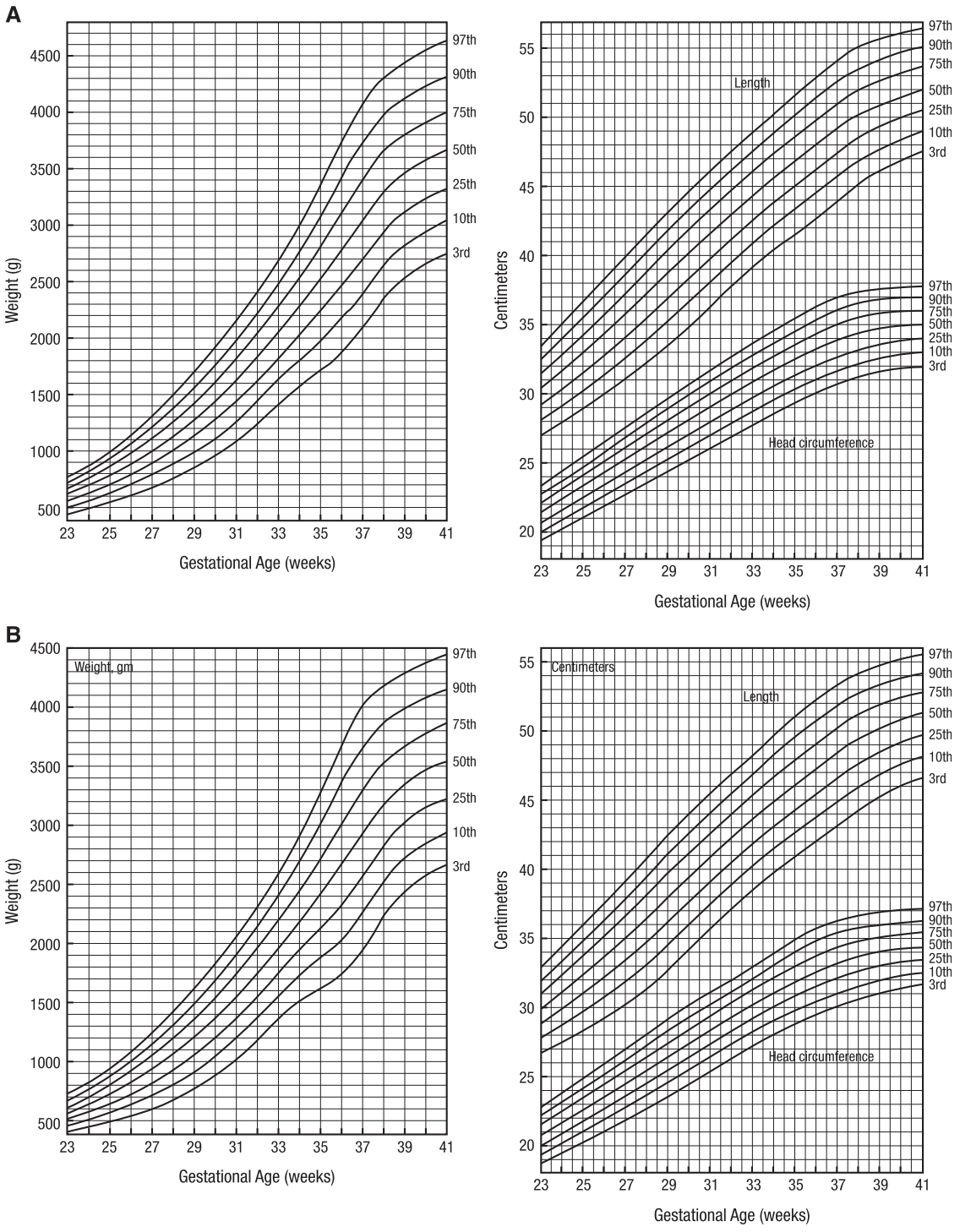

Figure 8. Intrauterine growth curves and SGA assessment for **A,** boys and **B,** girls.[38] (Reproduced with permission from Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. New intrauterine growth curves based on United States data. Pediatrics 2010; 125:e214-24. Copyright © 2010 American Academy of Pediatrics.)

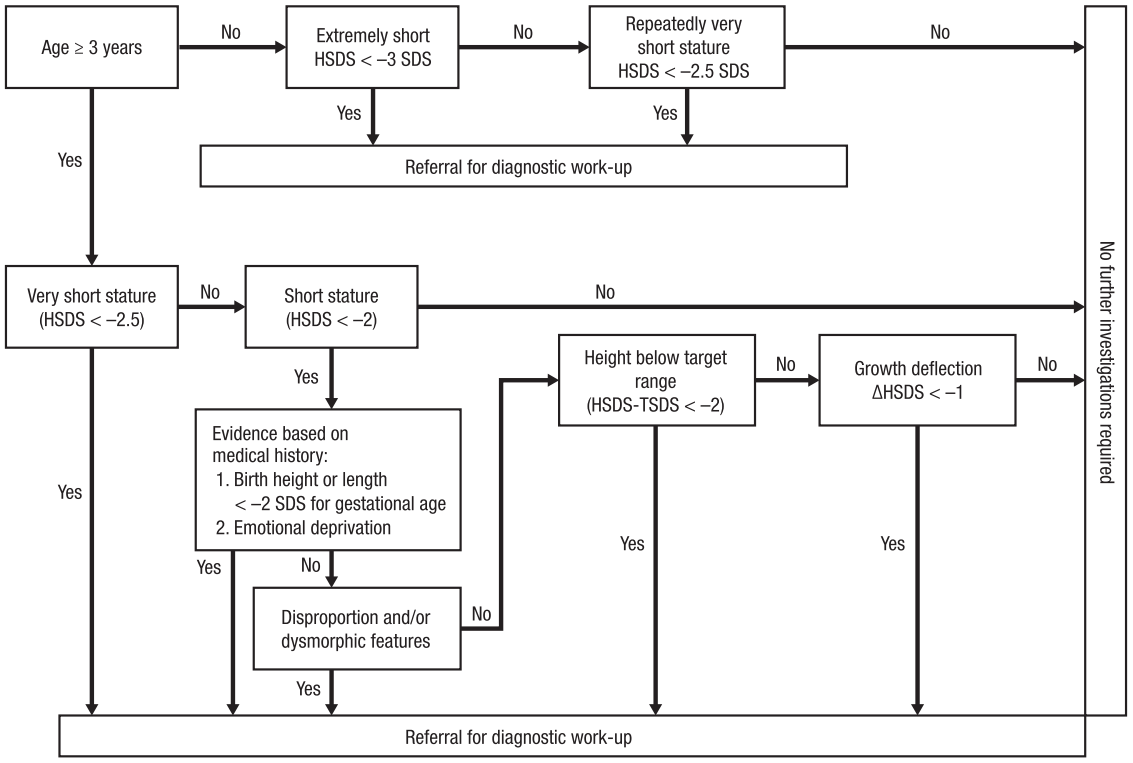

Figure 9. Flow diagram of proposed criteria for referral of children with growth disorders.[81] *HSDS*, height SDS; *THSDS*, target height SDS. (Reproduced from with permission from Grote FK, van Dommelen P, Oostdijk W, de Muinck Keizer-Schrama SM, Verkerk PH, Wit JM, et al. Developing evidence-based guidelines for referral for short stature. Arch Dis Child 2008; 93:212-7. Copyright © BMJ Publishing Group Ltd.)