Diagnosis of growth hormone deficiency in children

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INTRODUCTION

Growth hormone (GH) has been available for management of the short stature associated with GH deficiency (GHD) for more than 60 years [1]; recombinant DNA-derived human GH (rhGH) has been available since 1985. While availability is no longer a problem, there still remains a number of difficulties with the diagnosis of GHD, resulting mainly from the lack of appropriate tools to make (or exclude) the diagnosis reliably.

The incidence of short stature associated with GHD has been estimated to be approximately 1:4000 to 1:10,000 [2-4]. It is the primary indication for human GH treatment in childhood, which entails years of treatment with subcutaneous injections and substantial cost for the health care system. Based on these premises, it is clear that an accurate diagnosis is essential [5,6].

The diagnosis of GHD in children is reviewed here. Related content is in the following UpToDate topic reviews:

- (See "Causes of short stature".)
- (See "Diagnostic approach to children and adolescents with short stature".)
- (See "Treatment of growth hormone deficiency in children".)

AUXOLOGY

The diagnosis of GHD in childhood is based on a comparison of the child's growth pattern with established norms. A consensus view concluded that clinical assessment of the growth-retarded child is the single most useful parameter in diagnosing growth disorders and challenged the status of human GH measurements as the diagnostic "gold standard" [7].

- **Technique** – Neonates and children younger than two years may be difficult to measure accurately; the neonatometer (length stadiometer) and supine table are the recommended devices to reduce errors in measuring (figure 1). The vertical stadiometer is used to measure standing height, which is recommended for children two to three years or older (figure 2) [8].

  Errors in length or height measurements may be the result of unreliable equipment. For this reason, all apparatus should be checked frequently. More often, measuring procedures are at fault, perhaps in the positioning of the subject or in locating proper landmarks. (See "Measurement of growth in children".)

- **Growth charts** – Length or height data should be plotted on the appropriate growth chart. Length is for children measured lying down and should be used up to two to three years of age (figure 3A-B); height is for children measured standing and should be used for children over two to three years (figure 4A-B). The severity of short stature is quantified by determining the height percentiles or Z-scores from these charts or from calculators for boys (calculator 1) or for girls (calculator 2).

- **Height velocity** – Height velocity can be calculated from serial height determinations and plotted on appropriate velocity charts (figure 5A-B). A period of at least six months is necessary for reliable calculation of height velocity of children above the age of two years. (See "Diagnostic approach to children and adolescents with short stature", section on 'Evaluation of growth'.)

MOLECULAR GENETICS OF GROWTH HORMONE DEFICIENCY

Approximately 3 to 30 percent of children with GHD have an affected parent, sibling, or child [9,10]. Several genetic causes of GHD have been described [3] (see "Causes of hypopituitarism", section on 'Genetic diseases'):

- *POU1F1* – The *POU1F1* gene (known as *Pit1* in rodents) is responsible for pituitary-specific transcription of genes for GH, prolactin, thyrotropin, and the GH-releasing hormone (GHRH) receptor [11,12]. Pathogenic variants of the *POU1F1* gene are transmitted as autosomal recessive or codominant traits and cause variable peptide hormone

deficiencies with or without anterior pituitary hypoplasia, known as combined pituitary hormone deficiency (CPHD) type 1 (MIM #613038) [13-15]. One specific variant at the *POU1F1* locus has been associated with dominantly inherited isolated GHD [16].

- *PROP1* – Pathogenic variants in *PROP1* result in failure to activate *POU1F1*/*Pit1* gene expression and probably cause pituitary hypoplasia and/or familial multiple pituitary hormone deficiency [17]; paradoxical cystic hyperplasia of the pituitary also has been reported [18]. This is the most common known genetic cause of CPHD type 2 (MIM #262600) [19,20].

- Other transcription factors – In addition to *POU1F1*/*Pit1* and *PROP1*, other transcription factors participate in the differentiation of anterior pituitary cells. Pathogenic variants in these genes also cause congenital deficiencies of multiple pituitary hormones, with variable phenotypes. These include several syndromic manifestations [21]:

  - Septo-optic dysplasia (*HESX1*, *SOX2*, *SOX3*, *OTX2* and others)
  - CPHD with sensorineural deafness (MIM #221750, due to *LHX3*)
  - CPHD with/without cerebellar defects (MIM #262700, due to *LHX4*)
  - Optic nerve hypoplasia, polydactyly, midface defects (MIM #615849, due to *GLI2*)

- GHRH receptor gene defects – Children with pathogenic variants in the GHRH receptor gene (*GHRHR*) have undetectable GH release during standard provocative tests and after exogenous GHRH administration, but they respond to GH treatment.

- *GH1* – *GH1* is the gene encoding GH, located on chromosome 17. Gene deletions, frameshift variants, and nonsense variants of *GH1* have been described as causes of familial GHD [22].

- Syndrome of bioinactive GH – A diagnosis of the syndrome of bioinactive GH (Kowarski syndrome; MIM #262650) has been proposed for short children with a phenotype that resembles that of isolated GHD, with normal or slightly elevated basal GH levels in combination with low insulin-like growth factor 1 (IGF-1) concentrations that increase after treatment with exogenous GH. True molecular abnormalities involving a mutant GH molecule have rarely been reported [23,24].

Other pathogenic variants can cause GH insensitivity. The clinical phenotype of GH insensitivity is similar to that of GHD, but the mechanisms, laboratory findings, and treatment are different. (See "Growth hormone insensitivity syndromes", section on 'Introduction'.)

CLINICAL PRESENTATION

GHD can be divided into congenital and acquired forms. The single most important clinical manifestation of GHD is growth failure, and careful documentation of height velocity is critical to making the correct diagnosis. In some children with congenital GHD or hypopituitarism, the growth faltering may not be manifested until late infancy, as noted below.

Congenital — Patients with congenital severe GHD have only a slightly reduced birth length and may not immediately show growth failure. There is a higher frequency of breech presentation and perinatal asphyxia.

The clinical presentation depends upon the severity of the GHD. If GHD is congenital and severe, the diagnosis is relatively easy to confirm. Affected children present with hypoglycemia, microphallus (males), prolonged conjugated hyperbilirubinemia, frontal bossing, midface hypoplasia, hypotonia, central distribution of body fat, high-pitched voice, and very low serum concentrations of insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3). Postnatal growth is abnormal, and growth failure can occur during the first months of life [25-28] but may not be obvious until 6 to 12 months of age, by which time the height velocity is definitely slow and deviates from the normal growth curve, with length measurements often significantly below the mean. Bone age becomes delayed but is similar to height age, unless there is concurrent hypothyroidism.

In some children, congenital GHD is associated with multiple pituitary hormone deficiencies, which affect the clinical manifestations. When GHD is combined with deficiency of adrenocorticotropic hormone (ACTH), hypoglycemia may be severe. The combination of GHD with gonadotropin deficiency can cause microphallus, cryptorchidism, and hypoplasia of the scrotum.

Some children with congenital GHD have associated pathologic variants in one of several genes related to pituitary development or hormone formation, or with a structural brain abnormality. Others have no identifiable cause. (See 'Molecular genetics of growth hormone deficiency' above and "Causes of short stature", section on 'Growth hormone deficiency'.)

Acquired — Children with acquired GHD present with severe growth failure, delayed bone age, and increased weight:height ratios. Causes of acquired GHD include intracranial tumors involving the hypothalamic-pituitary region (eg, craniopharyngioma), cranial irradiation, and head trauma.

WHICH CHILDREN REQUIRE EVALUATION?

Children with short stature should be evaluated with careful serial measurements of length or height and compared with reference standards. (See 'Auxology' above.)

The clinical significance of the short stature depends on many factors, especially height velocity, severity of the short stature, and genetic potential. Many children with moderate short stature and normal growth (eg, height velocity at least 5 cm/year between four and six years of age and at least 4 cm/year between six years and puberty) require only a basic evaluation (including bone age evaluation), as outlined in a separate topic review. (See "Diagnostic approach to children and adolescents with short stature".)

A more comprehensive evaluation is warranted in children with one or more of the following features:

- Growth failure – This is suggested if a height-for-age curve has deviated downward across two major height percentile curves (eg, from above the 25th percentile to below the 10th percentile) or if the child is growing slower than the following rates:
  - Age two to four years – Height velocity less than 5.5 cm/year (<2.2 inches/year)
  - Age four to six years – Height velocity less than 5 cm/year (<2 inches/year)
  - Age six years to puberty:
    - Height velocity less than 4 cm/year for boys (<1.6 inches/year)
    - Height velocity less than 4.5 cm/year for girls (<1.8 inches/year)
- Severe short stature (eg, height ≤-2.5 standard deviations [SD], ie, 0.6th percentile), or less severe short stature combined with growth failure [29].
- Features that raise concerns for hypothalamic-pituitary dysfunction, either congenital (eg, hypoglycemia, microphallus, cryptorchidism, or wandering nystagmus) or acquired (eg, intracranial tumor, cranial irradiation, or head trauma), with decelerating growth, even if the child's height is within the normal range [7].
- Evidence for deficits in other hypothalamic-pituitary hormones, either congenital or acquired.

DIAGNOSTIC APPROACH

Once the decision to evaluate a short child has been made, a variety of different tests can be performed.

The first step is to evaluate for other causes of growth failure, including chronic systemic disease, hypothyroidism, Turner syndrome (in girls), and skeletal disorders. This is accomplished through a thorough medical history and physical examination. Laboratory evaluation should be performed when appropriate, including screens for systemic disease, undernutrition, inflammation, and thyroid function, and a karyotype in girls to rule out Turner syndrome. (See "Diagnostic approach to children and adolescents with short stature", section on 'Laboratory and imaging studies'.)

If there is no evidence of these disorders, then the possibility of GHD should be investigated with the following tests:

- Insulin-like growth factor 1 (IGF-1)
- Insulin-like growth factor binding protein-3 (IGFBP-3)
- Bone age (if not done previously)

GHD is effectively excluded in children with a normal bone age and height velocity. In this case, provocative testing for GHD is not required.

When GHD is congenital and near complete, the diagnosis is relatively easy to confirm because affected children present with severe growth failure, delayed bone age, and very low serum concentrations of GH, IGF-1, and IGFBP-3 [7]. For patients with all of these clinical characteristics, it is reasonable to make the diagnosis of GHD without performing GH stimulation testing.

Milder degrees of growth faltering and decreased IGF-1 and IGFBP-3 levels are consistent with GHD but are also consistent with other causes of growth failure, including poor nutrition. (See 'IGF-1 and IGFBP-3' below.)

If not explicable on the basis of undernutrition, low IGF-1 and/or IGFBP-3 levels are strongly suggestive of a diagnosis of GHD, but this should be confirmed by provocative GH testing. In addition, a magnetic resonance imaging (MRI) of the hypothalamic-pituitary region (with and without contrast) is recommended for children with suspected GHD [30]. (See 'Growth hormone stimulation tests' below and 'Imaging' below.)

TESTING FOR GROWTH HORMONE DEFICIENCY

Assessment of pituitary GH production is difficult because GH secretion is pulsatile, with the most consistent surges during stages 3 and 4 of sleep. The regulation of GH secretion involves at least two well-studied hypothalamic factors, GH-releasing hormone (GHRH; stimulatory) and somatostatin (inhibitory). In addition, GH secretion is influenced by multiple other peptides and neurotransmitters, including ghrelin (stimulatory) produced both in the hypothalamus and in the stomach, which causes stimulation of GHRH [31].

Between normal pulses of GH secretion, serum GH levels are low, often below the limits of sensitivity of most conventional assays. Thus, measurement of a random serum GH level is not helpful in diagnosing GHD and is used only to exclude the possibility of GH insensitivity.

Because of these issues, the diagnosis of GHD is made with a combination of clinical assessment and auxology, insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) levels, and GH stimulation tests.

IGF-1 and IGFBP-3 — The determination of IGF-1 and IGFBP-3 levels has become a widely used tool in the diagnostic evaluation of growth disorders. IGF-1 is the mediator of the majority of the growth-promoting actions of GH. (See "Physiology of insulin-like growth factor 1".)

Test characteristics — Two benefits of measurement of serum concentrations of IGF-1 and IGFBP-3 are:

- Their concentrations often reflect the integrated concentration of secreted GH
- Unlike the pulsatile secretion of GH, IGF-system peptides are stable during the day (serum half-lives of 12 to 16 hours) [32]

Despite relatively good correlations within groups of patients between GH secretion and IGF-1 concentrations [33-36], there remain substantial problems in assessing GH status by measurement of IGF-1 alone in individual patients [37,38]:

- Normal IGF-1 values in children younger than three years may be very low and, in some cases, may be below the lower limit of detection of the assay. As a result, the normal range overlaps with that for GHD. Newer assays using mass spectrometry may resolve this issue [39].

- Inadequate nutrition lowers IGF-1 concentrations despite normal or even elevated levels of GH.

- Serum IGF-1 levels may be low in conditions other than GHD, such as GH insensitivity, hypothyroidism [40], diabetes [41], renal failure [40,42], and cancer [43].

Of the six IGFBPs, IGFBP-3 is the major serum carrier protein for IGF-1 [44-46] and the most GH-dependent [47]. IGFBP-3 levels are less nutritionally dependent and are more discriminatory than those of IGF-1 in the lower end of the normal range. Although levels of both IGF-1 and IGFBP-3 normally increase with age, IGFBP-3 is a better screening test for GHD than IGF-1 in younger children because it is easier to distinguish low-normal levels of IGFBP-3 in young children from truly low levels [48]. (See "Physiology of insulin-like growth factor 1".)

Interpretation of results — For patients with growth failure or severe short stature, we interpret the results of this testing as follows:

- **Moderately or severely reduced** IGF-1 and IGFBP-3 (eg, <-2 standard deviations [SD]) **with** delayed bone age:
  - In most cases, the possibility of GHD should be explored by provocative GH testing, if other causes of low IGF-1 and IGFBP-3, such as poor nutrition, have been excluded. (See 'Growth hormone stimulation tests' below.)
  - If the growth failure is severe, bone age is significantly delayed, and IGF-1 and IGFBP-3 are definitively low (eg, <-2 SD), it is reasonable to make the diagnosis of GHD without performing GH stimulation testing, especially in the setting of known hypothalamic-pituitary disease and/or its treatment (eg, brain surgery and/or radiation).
- **Somewhat low** IGF-1 and IGFBP-3 (eg, between 0 and -2 SD) – The decision about whether to perform provocative GH testing depends on individual patient characteristics, including the severity of growth failure, degree of bone age delay, and whether the low levels can be explained by other factors, such as poor nutrition.
- **Clearly normal** IGF-1 and IGFBP-3 (SD ≥0); ie, in the upper one-half of the normal range – GHD is extremely unlikely, and no further testing is required.

If the results of IGF-1 and IGFBP-3 are discordant, IGF-1 takes precedence, except for infants and young children, in whom IGFBP-3 should guide the decision about further testing. IGF-1 and IGFBP-3 levels should be interpreted against reference ranges that are standardized for sex and age (or better, by stage of sexual maturation, if available). The range varies with the assay used, and results should be interpreted against standards provided by the laboratory performing the test [49]. Consideration of norms based on bone age rather than chronologic age has also been recommended.

Growth hormone stimulation tests

Indications — Provocative (stimulation) GH testing is indicated for most patients to confirm a diagnosis of GHD. Because this testing has limitations, the results should **not** be used as the sole diagnostic criterion and should be interpreted in the context of auxologic findings, bone age, and IGF-1 and IGFBP-3 concentrations [50,51].

Provocative GH testing is **not** necessary for selected patients in whom other clinical criteria are sufficient to make the diagnosis of GHD, including those with the following conditions:

- Pituitary abnormality (secondary to a congenital anomaly, tumor, or irradiation) and a known deficiency of at least one other pituitary hormone, as well as auxologic criteria [52].
- Newborn with a congenital pituitary abnormality (ectopic posterior pituitary and pituitary hypoplasia with abnormal stalk) or known deficiency of a pituitary hormone, along with hypoglycemia, at which time a simultaneous serum GH concentration is <5 mcg/L [52].
- Infant or young child with extreme short stature (eg, height <-3 SD), normal nutrition, significantly reduced IGF-1 (eg, <-2 SD) and IGFBP-3, and delayed bone age. This is the classic presentation of congenital and severe GHD, and most experts agree that provocative testing is not required to make the diagnosis.

Provocative testing also is not necessary for short children with a normal bone age and height velocity or for those with clearly normal levels of IGF-1 and IGFBP-3. These findings are sufficient to exclude GHD without provocative testing. (See 'Which children require evaluation?' above and 'Interpretation of results' above.)

Limitations — Provocative GH testing has a number of limitations (table 1) [7,51]:

- The tests are nonphysiologic.
- The cutoff level of "normal" is arbitrary and may depend on the specific provocative agent used.
- The interpretation of the test results depends upon age and sex hormone concentrations [51,53]. Children with constitutional delay of growth and puberty may have low GH results on provocative testing in the absence of true GHD (ie, false-positive results). Administration of sex steroids for a few days prior to the provocative GH testing (known as "priming") reduces the chance of a false-positive result, as discussed below [50,51].
- Adiposity (as measured by body mass index) also influences GH response to the stimulation test, such that obese children show diminished GH responses to all stimuli [52,54,55].

- The tests rely upon GH assays of variable accuracy.
- The tests are expensive, uncomfortable, and carry some risks.
- Test reproducibility has not been adequately documented.
- The ability of the tests to discriminate between normal short children and children with partial GHD is limited.

Because of these limitations, it is clear that there is no real "gold standard" for the diagnosis of GHD [30,51]. Nonetheless, GH stimulation testing is a valuable diagnostic tool when combined with auxologic data and measurements of IGF-1 and IGFBP-3. The peak GH response to provocative testing is also a useful predictor of response during the first year of treatment with GH [56,57].

Technique — Measurement of GH secretory reserve relies upon the use of physiologic or pharmacologic stimuli.

- **General protocol** – The stimulation tests are performed after an overnight fast. After the pharmacologic agent is administered, serum samples are collected at intervals designed to capture the peak stimulated GH level; the expected time to this peak varies depending on the stimulus. Traditionally, most pediatric endocrinologists defined a "normal" response by a serum GH concentration of >10 mcg/L, but a cutoff of 7.5 mcg/L is often used for modern assays and is used in some countries [50]. Newer published data [58] suggest that assay-specific cutoffs to define GHD may be necessary [50,59]. Specific considerations for the measurement of human GH have been reviewed in detail [60].

  Some clinicians also measure a baseline GH level as part of the stimulation test. If that level is in the upper one-half of the unstimulated reference range (eg, between 5 and 10 mcg/L), this suggests that GHD is unlikely and that subsequent GH values after stimulation, even if the values are all <10 mcg/L, may not necessarily reflect true GHD. This is because of an absolute and then relative refractory period after a physiologic GH pulse.

- **Choice of stimulus** – There is general consensus that two different stimuli should be used for most patients [50,52]. In a patient with known pathology of the central nervous system, other pituitary hormone defects, or a genetic defect, one test is sufficient to establish the diagnosis [30,51,61]. The pharmacologic stimulants that have the highest specificity (fewest false-positive results) and are most commonly used clinically are:

  - Clonidine – Clonidine stimulates GH by several mechanisms, including the stimulation of GHRH via alpha-adrenergic pathways. It is administered orally at a dose of 5 mcg/kg

(maximum 250 mcg), and serum GH is measured at 0, 30, 60 and 90 minutes; peak GH secretion typically occurs approximately one hour after the stimulus is given [61]. Clonidine may cause modest hypotension and hypoglycemia, so patients should be monitored for these problems during the test. This stimulant is thought to have relatively good specificity, although estimates of this test's sensitivity and specificity vary [62-65].

- Arginine – An intravenous infusion of 0.5 g/kg body weight (to a maximum of 40 g) is given over 30 minutes, and serum GH is measured at 0, 30, 60, 90, and 120 minutes [61]. The maximum GH peak is expected at approximately 60 minutes. There are no side effects from this test, but overdoses have been described. GH secretion can be enhanced (and therefore false-positive results reduced) by adding a dose of L-Dopa orally just prior to the administration of arginine [61]. However, L-Dopa is not available in the United States. L-Dopa also can be used alone but is a relatively weak stimulant of GH release.

- Glucagon – Administration of glucagon causes transient hyperglycemia, which in turn stimulates endogenous insulin secretion, followed by controlled hypoglycemia and consequent GH secretion [61,66,67]. It is less risky than insulin-induced hypoglycemia (described below) and is a good choice for infants and young children. Glucagon is administered subcutaneously at a dose of 0.03 mg/kg (maximum 1 mg), and serum samples are drawn at intervals between one and three hours after the stimulus. Peak GH secretion occurs between two and three hours after glucagon administration; side effects are mild and transient and include nausea, vomiting, sweating, or headaches.

- Insulin-induced hypoglycemia – Insulin-induced hypoglycemia is a potent stimulant of GH release and is therefore among the most specific tests for GHD [68-70]. Regular insulin is administered intravenously at a dose of 0.05 to 0.1 unit/kg. The maximum GH peak is expected at 15 to 30 minutes after insulin administration. Serum GH is measured at 0, 15, 30, 45, and 90 minutes. However, this test is infrequently used in children because of safety concerns [30]. (See "Growth hormone deficiency in adults", section on 'Insulin-induced hypoglycemia'.)

Arginine, glucagon, and insulin also provide information about the hypothalamic-pituitary-adrenal axis.

- Other – Macimorelin acetate is used for testing adults with suspected GHD, but there are few data in the pediatric population, although it is under study. The performance of

this and other provocative tests is discussed separately. (See "Growth hormone deficiency in adults", section on 'Provocative tests'.)

- **Sex steroid priming** – Administration of sex steroids prior to the GH stimulation test (known as "priming") increases the response to the stimulus and diminishes the possibility of a false diagnosis of GHD [51,71]. The clinical utility of priming has not been fully established, but guidelines recommend priming before provocative GH testing in prepubertal boys older than 11 years and prepubertal girls older than 10 years [52]. Priming is most useful for otherwise healthy patients with mild growth failure (eg, predicted adult height within -2 SD of the mean) because it may reduce false-positive results for GH stimulation testing and thus help distinguish mild GHD from constitutional delay of growth and puberty.

- **Other considerations** – Stimulation testing with the combination of GHRH and arginine improves the evaluation for patients with multiple pituitary hormone deficiencies to determine the level of the secretory defect [61,72]. However, it is not useful in making a diagnosis of GHD in children with isolated idiopathic GHD (which accounts for most children with GHD), because these children have a defect in hypothalamic regulation of pituitary GH secretion and are expected to respond normally to GHRH. GHRH is not available in the United States.

  If the child is also hypothyroid, the tests of GH secretion should be postponed until thyroxine is adequately replaced. GH secretion may be subnormal merely as a result of the hypothyroidism. Thus, hypothyroidism should be excluded before performing GH stimulation tests. (See 'Diagnostic approach' above.)

Imaging — High-quality contrast-enhanced MRI with fine cuts (1 mm) permits excellent visualization of the hypothalamic-pituitary stalk (infundibulum). On T1-weighted imaging, a clear demarcation can be made between the adenohypophysis (after two months of age) and the neurohypophysis, which appears as hyperintense [73]. Newer techniques may permit imaging without contrast sequences [74].

After the clinical and biochemical diagnosis of GHD is made, it is essential to obtain an MRI of the brain with narrow cuts through the hypothalamic-pituitary area [30]. This imaging is important to exclude the possibility of a pituitary tumor; it also permits diagnostic characterization by showing the presence or absence of morphologic abnormalities such as anterior pituitary hypoplasia, pituitary stalk agenesis, and posterior pituitary ectopia.

An MRI is helpful in the prediction of permanent GHD. In one study, GH secretion was reevaluated after completion of GH treatment in young adults with childhood-onset GHD

[74,75]. GHD was permanent in children with congenital hypothalamic-pituitary abnormalities on MRI scans, while children without hypothalamic-pituitary abnormalities frequently showed normalization of GH secretion at the completion of GH treatment.

An MRI may also provide evidence of severe GHD if the diagnosis of pituitary stalk interruption syndrome is made [75]. This entity consists of ectopic neurohypophysis, interrupted pituitary stalk, and hypoplastic adenohypophysis and has been associated with severe GHD.

If an MRI is not available, computed tomography (CT) of the head is sufficient to screen for a pituitary tumor.

GROWTH HORMONE INSENSITIVITY

GH insensitivity is a group of inherited disorders in which there is a reduction or absence of the biologic effects of GH despite normal or above-normal production of GH. GH insensitivity should be suspected in patients with growth failure and low insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) levels, but normal or increased circulating levels of GH, and lack of response to GH (algorithm 1).

The classic GH insensitivity syndrome is also known as Laron syndrome (formerly, Laron dwarfism), in which pathogenic variants of the gene encoding the GH receptor cause severe postnatal growth failure. Lesser degrees of GH resistance may play a role in a small percentage of cases of idiopathic short stature [76] (see "Growth hormone treatment for idiopathic short stature", section on 'Dose adjustment for IGF-1 levels'). This disorder is discussed in a separate topic review. (See "Growth hormone insensitivity syndromes".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Growth hormone deficiency and other growth disorders".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given

condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: My child is short (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Pathogenesis** – Growth hormone deficiency (GHD) can be caused by a variety of pathogenic variants (although these are rare) or by conditions affecting hypothalamic or pituitary function. GHD may be isolated or may occur in association with deficiencies of other pituitary hormones. (See 'Molecular genetics of growth hormone deficiency' above and 'Clinical presentation' above.)

- **Candidates for evaluation** – GHD should be suspected in patients with marked short stature (more than 2.5 standard deviations [SD] below the mean) and/or marked growth failure (height velocity less than the 25th percentile for age), or more moderate degrees of short stature and growth failure with decelerating growth (without alternative explanation). It should also be suspected in children with signs or symptoms of hypothalamic-pituitary dysfunction with decelerating growth. (See 'Which children require evaluation?' above.)

- **Diagnostic approach** – GHD is primarily a clinical diagnosis, based upon auxologic features and confirmed by biochemical testing.

  - **Clinical evaluation** – The first step is to evaluate for causes of growth failure other than GHD, including chronic systemic disease, hypothyroidism, Turner syndrome (in girls), and skeletal disorders. This is accomplished through a thorough medical history and physical examination. Laboratory evaluation should be performed when appropriate. (See 'Which children require evaluation?' above and "Diagnostic approach to children and adolescents with short stature".)

- **Initial testing** – Patients with suspected GHD should be screened with radiographic measurement of bone age, insulin-like growth factor 1 (IGF-1), and insulin-like growth factor binding protein-3 (IGFBP-3). We interpret the results of IGF-1 and IGFBP-3 testing as follows (see 'Interpretation of results' above):

  - Clearly normal IGF-1 and IGFBP-3 (SD ≥0; ie, in the upper one-half of the normal range) – GHD is extremely unlikely, and no further testing is required.

  - Somewhat low IGF-1 (eg, SD between 0 and -2) and IGFBP-3 – Moderate suspicion of GHD. The decision about whether to perform provocative GH testing depends on individual patient characteristics, including the severity of growth failure, degree of bone age delay, and whether the low levels of IGF-1 and IGFBP-3 can be explained by other factors, such as poor nutrition.

  - Moderately or severely reduced IGF-1 (eg, SD <-2) and IGFBP-3 **with** delayed bone age – Strong suspicion of GHD. In most cases, the possibility of GHD should be explored by provocative GH testing, if other causes of low IGF-1 and IGFBP-3, such as poor nutrition, have been excluded. (See 'Growth hormone stimulation tests' above.)

- **Additional tests for selected patients**

  - **Stimulation tests** – GH stimulation tests are required to make a definitive diagnosis of GHD in children with suspected isolated GHD (ie, with no evidence of other pituitary hormone deficiencies); testing with two different provocative tests is recommended to establish the diagnosis. Clonidine, arginine, and glucagon are common choices in children. Hypothyroidism should be excluded first by performing thyroid function tests. Provocative GH testing has a number of limitations (table 1). (See 'Growth hormone stimulation tests' above.)

    GH stimulation testing is **not** necessary for selected patients in whom other clinical criteria are sufficient to make the diagnosis of GHD, including those with a known pituitary abnormality (congenital anomaly, tumor, or irradiation) and known deficiency of at least one other pituitary hormone, with marked growth failure. (See 'Indications' above.)

  - **Imaging** – If GHD is confirmed, MRI of the hypothalamic-pituitary area is recommended to rule out tumors, investigate for structural causes of GHD, and evaluate the severity and prognosis of the deficiency. (See 'Imaging' above.)

REFERENCES

1. RABEN MS. Treatment of a pituitary dwarf with human growth hormone. J Clin Endocrinol Metab 1958; 18:901.
2. Rona RJ, Tanner JM. Aetiology of idiopathic growth hormone deficiency in England and Wales. Arch Dis Child 1977; 52:197.
3. Murray PG, Dattani MT, Clayton PE. Controversies in the diagnosis and management of growth hormone deficiency in childhood and adolescence. Arch Dis Child 2016; 101:96.
4. Human growth hormone (somatotropin) for the treatment of growth failure in children, NIC E, 2010. http://www.nice.org.uk/guidance/TA188 (Accessed on January 05, 2016).
5. Strasburger CJ, Wu Z, Pflaum CD, Dressendörfer RA. Immunofunctional assay of human growth hormone (hGH) in serum: a possible consensus for quantitative hGH measurement. J Clin Endocrinol Metab 1996; 81:2613.
6. Houchin LD, Rogol AD. The therapeutic efficacy and use of growth hormone-releasing hormone in the treatment of idiopathic growth hormone deficiency. Today's Therapeutic Trends 1999; 17:85.
7. Rosenfeld RG, Albertsson-Wikland K, Cassorla F, et al. Diagnostic controversy: the diagnosis of childhood growth hormone deficiency revisited. J Clin Endocrinol Metab 1995; 80:1532.
8. Rogol AD, Hayden GF. Etiologies and early diagnosis of short stature and growth failure in children and adolescents. J Pediatr 2014; 164:S1.
9. Pérez Jurado LA, Argente J. Molecular basis of familial growth hormone deficiency. Horm Res 1994; 42:189.
10. Phillips JA 3rd, Cogan JD. Genetic basis of endocrine disease. 6. Molecular basis of familial human growth hormone deficiency. J Clin Endocrinol Metab 1994; 78:11.
11. Mangalam HJ, Albert VR, Ingraham HA, et al. A pituitary POU domain protein, Pit-1, activates both growth hormone and prolactin promoters transcriptionally. Genes Dev 1989; 3:946.
12. Li S, Crenshaw EB 3rd, Rawson EJ, et al. Dwarf locus mutants lacking three pituitary cell types result from mutations in the POU-domain gene pit-1. Nature 1990; 347:528.
13. Cohen LE, Wondisford FE, Salvatoni A, et al. A "hot spot" in the Pit-1 gene responsible for combined pituitary hormone deficiency: clinical and molecular correlates. J Clin Endocrinol Metab 1995; 80:679.

14. Pellegrini-Bouiller I, Bélicar P, Barlier A, et al. A new mutation of the gene encoding the transcription factor Pit-1 is responsible for combined pituitary hormone deficiency. J Clin Endocrinol Metab 1996; 81:2790.
15. Gregory LC, Cionna C, Cerbone M, Dattani MT. Identification of genetic variants and phenotypic characterization of a large cohort of patients with congenital hypopituitarism and related disorders. Genet Med 2023; 25:100881.
16. Sobrier ML, Tsai YC, Pérez C, et al. Functional characterization of a human POU1F1 mutation associated with isolated growth hormone deficiency: a novel etiology for IGHD. Hum Mol Genet 2016; 25:472.
17. Wu W, Cogan JD, Pfäffle RW, et al. Mutations in PROP1 cause familial combined pituitary hormone deficiency. Nat Genet 1998; 18:147.
18. Zygmunt-Górska A, Starzyk J, Adamek D, et al. Pituitary enlargement in patients with PROP1 gene inactivating mutation represents cystic hyperplasia of the intermediate pituitary lobe. Histopathology and over 10 years follow-up of two patients. J Pediatr Endocrinol Metab 2009; 22:653.
19. Obermannova B, Pfaeffle R, Zygmunt-Gorska A, et al. Mutations and pituitary morphology in a series of 82 patients with PROP1 gene defects. Horm Res Paediatr 2011; 76:348.
20. Ziemnicka K, Budny B, Drobnik K, et al. Two coexisting heterozygous frameshift mutations in PROP1 are responsible for a different phenotype of combined pituitary hormone deficiency. J Appl Genet 2016; 57:373.
21. Cullingford DJ, Siafarikas A, Choong CS. Genetic Etiology of Congenital Hypopituitarism. [Updated 2023 Feb 5]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK586145/ (Accessed on September 26, 2023).
22. Madeira JL, Jorge AA, Martin RM, et al. A homozygous point mutation in the GH1 promoter (c.-223C>T) leads to reduced GH1 expression in siblings with isolated GH deficiency (IGHD). Eur J Endocrinol 2016; 175:K7.
23. Takahashi Y, Kaji H, Okimura Y, et al. Brief report: short stature caused by a mutant growth hormone. N Engl J Med 1996; 334:432.
24. Besson A, Salemi S, Deladoëy J, et al. Short stature caused by a biologically inactive mutant growth hormone (GH-C53S). J Clin Endocrinol Metab 2005; 90:2493.
25. Wit JM, van Unen H. Growth of infants with neonatal growth hormone deficiency. Arch Dis Child 1992; 67:920.

26. Gluckman PD, Gunn AJ, Wray A, et al. Congenital idiopathic growth hormone deficiency associated with prenatal and early postnatal growth failure. The International Board of the Kabi Pharmacia International Growth Study. J Pediatr 1992; 121:920.
27. De Luca F, Bernasconi S, Blandino A, et al. Auxological, clinical and neuroradiological findings in infants with early onset growth hormone deficiency. Acta Paediatr 1995; 84:561.
28. Pena-Almazan S, Buchlis J, Miller S, et al. Linear growth characteristics of congenitally GH-deficient infants from birth to one year of age. J Clin Endocrinol Metab 2001; 86:5691.
29. Kärkinen J, Miettinen PJ, Raivio T, Hero M. Etiology of severe short stature below -3 SDS in a screened Finnish population. Eur J Endocrinol 2020; 183:481.
30. Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. GH Research Society. J Clin Endocrinol Metab 2000; 85:3990.
31. Osterstock G, Escobar P, Mitutsova V, et al. Ghrelin stimulation of growth hormone-releasing hormone neurons is direct in the arcuate nucleus. PLoS One 2010; 5:e9159.
32. Martha PM Jr, Rogol AD, Veldhuis JD, et al. Alterations in the pulsatile properties of circulating growth hormone concentrations during puberty in boys. J Clin Endocrinol Metab 1989; 69:563.
33. Rosenfeld RG. Biochemical diagnostic strategies in the evaluation of short stature: the diagnosis of insulin-like growth factor deficiency. Horm Res 1996; 46:170.
34. Underwood LE. Clinical uses of IGF-1 and IGF binding protein assays. In: The IGF System: M olecular Biology, Physiology, and Clinical Applications, Rosenfeld RG, Roberts CT (Eds), Hum an Press Inc., New Jersey 1999. p.617.
35. Hasegawa Y, Hasegawa T, Aso T, et al. Comparison between insulin-like growth factor-I (IGF-I) and IGF binding protein-3 (IGFBP-3) measurement in the diagnosis of growth hormone deficiency. Endocr J 1993; 40:185.
36. Nunez SB, Municchi G, Barnes KM, Rose SR. Insulin-like growth factor I (IGF-I) and IGF-binding protein-3 concentrations compared to stimulated and night growth hormone in the evaluation of short children--a clinical research center study. J Clin Endocrinol Metab 1996; 81:1927.
37. Bancos I, Algeciras-Schimnich A, Grebe SK, et al. Evaluation of Variables Influencing the Measurement of Insulin-like Growth Factor-1. Endocr Pract 2014; 20:421.
38. Stanley TL, Feldpausch MN, Murphy CA, et al. Discordance of IGF-1 and GH stimulation testing for altered GH secretion in obesity. Growth Horm IGF Res 2014; 24:10.

39. Bonert V, Carmichael J, Wu Z, et al. Discordance between mass spectrometry and immunometric IGF-1 assay in pituitary disease: a prospective study. Pituitary 2018; 21:65.

40. Baxter RC, Brown AS, Turtle JR. Radioimmunoassay for somatomedin C: comparison with radioreceptor assay in patients with growth-hormone disorders, hypothyroidism, and renal failure. Clin Chem 1982; 28:488.

41. Tamborlane WV, Hintz RL, Bergman M, et al. Insulin-infusion-pump treatment of diabetes: influence of improved metabolic control on plasma somatomedin levels. N Engl J Med 1981; 305:303.

42. Powell DR, Rosenfeld RG, Baker BK, et al. Serum somatomedin levels in adults with chronic renal failure: the importance of measuring insulin-like growth factor I (IGF-I) and IGF-II in acid-chromatographed uremic serum. J Clin Endocrinol Metab 1986; 63:1186.

43. Chinceşan MI, Mărginean O, Pitea AM, Dobreanu M. Relationship of serum insulin-like growth factor I (IGF-I) with nutritional status in pediatric patients with malignant diseases--a single Romanian center experience. Eur J Pediatr 2013; 172:1401.

44. Rosenfeld RG, Lamson G, Pham H, et al. Insulinlike growth factor-binding proteins. Recent Prog Horm Res 1990; 46:99.

45. Lamson G, Giudice LC, Rosenfeld RG. Insulin-like growth factor binding proteins: structural and molecular relationships. Growth Factors 1991; 5:19.

46. Baxter RC, Martin JL. Binding proteins for the insulin-like growth factors: structure, regulation and function. Prog Growth Factor Res 1989; 1:49.

47. Baxter RC, Martin JL. Radioimmunoassay of growth hormone-dependent insulinlike growth factor binding protein in human plasma. J Clin Invest 1986; 78:1504.

48. Bhala A, Harris MC, Zirin S, et al. Insulin-like growth factor axis parameters in sick hospitalized neonates. J Pediatr Endocrinol Metab 1998; 11:451.

49. Examples of reference ranges from commonly used laboratories are available in the Interpretive Guide from Quest (www.questdiagnostics.com/hcp/index.html), or the Expected Values manual from Esoterix (www.esoterix.com/prodserv/test_menu/endocrinology.asp) www.questdiagnostics.com/hcp/index.html; www.esoterix.com/prodserv/test_menu/endocrinology.asp (Accessed on October 15, 2008).

50. Collett-Solberg PF, Ambler G, Backeljauw PF, et al. Diagnosis, Genetics, and Therapy of Short Stature in Children: A Growth Hormone Research Society International Perspective. Horm Res Paediatr 2019; 92:1.

51. Yuen KCJ, Johannsson G, Ho KKY, et al. Diagnosis and testing for growth hormone deficiency across the ages: a global view of the accuracy, caveats, and cut-offs for

diagnosis. Endocr Connect 2023; 12.

52. Grimberg A, DiVall SA, Polychronakos C, et al. Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency. Horm Res Paediatr 2016; 86:361.
53. Price DA. GH testing in KIGS: The clinical reality. In: Growth Hormone Therapy in KIGS-10 Years' Experience, Ranke MB, Wilton P (Eds), Huthig GmbH, Heidelberg-Leipzig, Germany 1999. p.73.
54. Lee HS, Hwang JS. Influence of body mass index on growth hormone responses to classic provocative tests in children with short stature. Neuroendocrinology 2011; 93:259.
55. Stanley TL, Levitsky LL, Grinspoon SK, Misra M. Effect of body mass index on peak growth hormone response to provocative testing in children with short stature. J Clin Endocrinol Metab 2009; 94:4875.
56. Cole TJ, Hindmarsh PC, Dunger DB. Growth hormone (GH) provocation tests and the response to GH treatment in GH deficiency. Arch Dis Child 2004; 89:1024.
57. Cohen P, Rogol AD, Howard CP, et al. Insulin growth factor-based dosing of growth hormone therapy in children: a randomized, controlled study. J Clin Endocrinol Metab 2007; 92:2480.
58. Ranke MB. Growth hormone deficiency: Diagnostic principles and practice. In: Diagnostics of endocrine function in children and adolescents, 4th ed, Ranke MB, Mullis P-E (Eds), Karger, Basel 2011. p.102.
59. Wagner IV, Paetzold C, Gausche R, et al. Clinical evidence-based cutoff limits for GH stimulation tests in children with a backup of results with reference to mass spectrometry. Eur J Endocrinol 2014; 171:389.
60. Bidlingmaier M, Freda PU. Measurement of human growth hormone by immunoassays: current status, unsolved problems and clinical consequences. Growth Horm IGF Res 2010; 20:19.
61. Richmond EJ, Rogol AD. Growth hormone deficiency in children. Pituitary 2008; 11:115.
62. Lanes R, Hurtado E. Oral clonidine-an effective growth hormone-releasing agent in prepubertal subjects. J Pediatr 1982; 100:710.
63. Fraser NC, Seth J, Brown NS. Clonidine is a better test for growth hormone deficiency than insulin hypoglycaemia. Arch Dis Child 1983; 58:355.
64. Al Khalifah R, Moisan L, Bui H. The shortened combined clonidine and arginine test for growth hormone deficiency is practical and specific: a diagnostic accuracy study. J Pediatr

Endocrinol Metab 2016; 29:305.

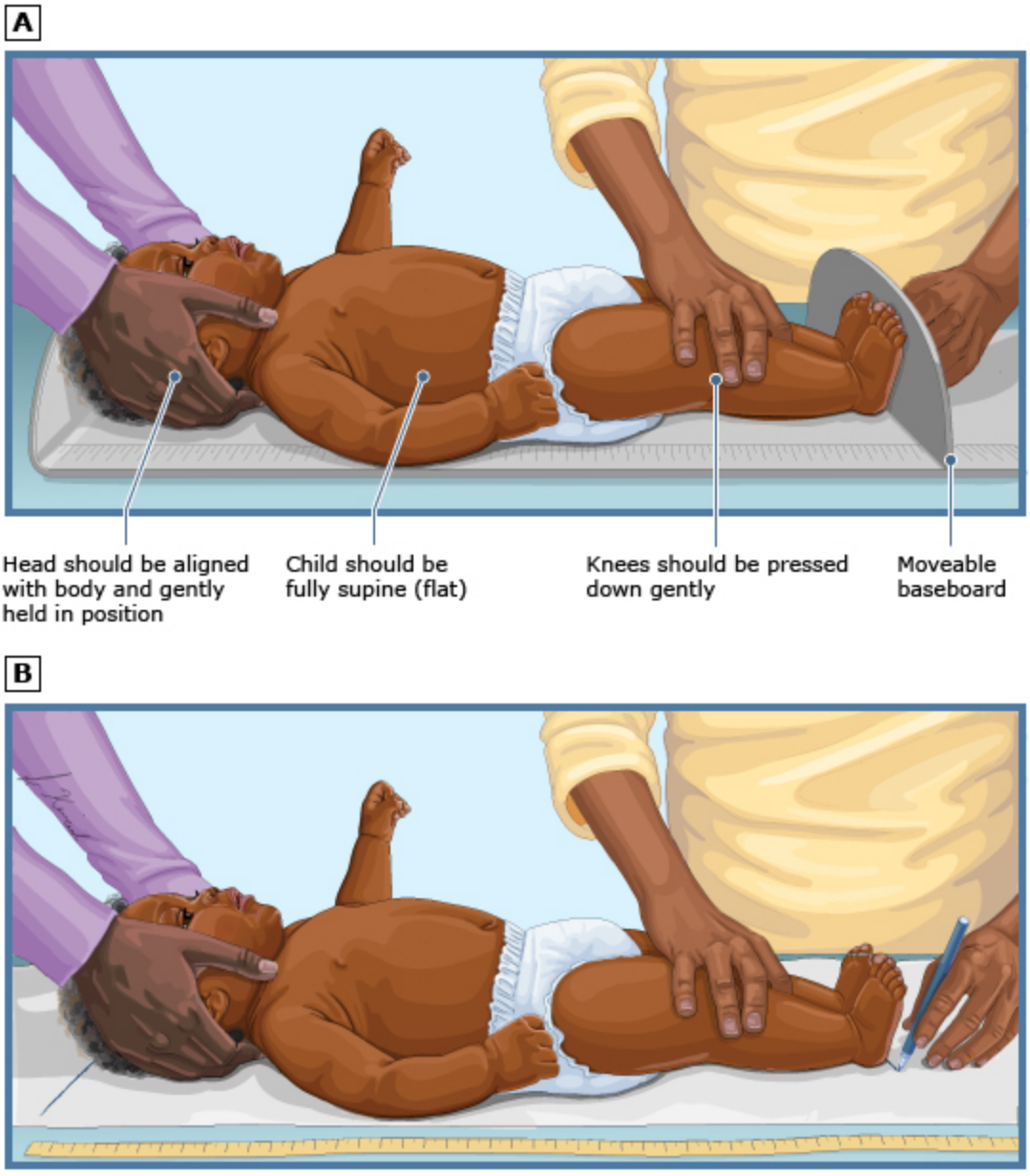
65. Obara-Moszyńska M, Kedzia A, Korman E, Niedziela M. Usefulness of growth hormone (GH) stimulation tests and IGF-I concentration measurement in GH deficiency diagnosis. J Pediatr Endocrinol Metab 2008; 21:569.
66. Mitchell ML, Byrne MJ, Sanchez Y, Sawin CT. Detection of growth-hormone deficiency. N Engl J Med 1970; 282:539.
67. Leong KS, Walker AB, Martin I, et al. An audit of 500 subcutaneous glucagon stimulation tests to assess growth hormone and ACTH secretion in patients with hypothalamic-pituitary disease. Clin Endocrinol (Oxf) 2001; 54:463.
68. Kaplan SL, Abrams CA, Bell JJ, et al. Growth and growth hormone. I. Changes in serum level of growth hormone following hypoglycemia in 134 children with growth retardation. Pediatr Res 1968; 2:43.
69. Root AW, Rosenfield RL, Bongiovanni AM, Eberlein WR. The plasma growth hormone response to insulin-induced hypoglycemia in children with retardation of growth. Pediatrics 1967; 39:844.
70. Raiti S, Davis WT, Blizzard RM. A comparison of the effects of insulin hypoglycaemia and arginine infusion on release of human growth hormone. Lancet 1967; 2:1182.
71. Marin G, Domené HM, Barnes KM, et al. The effects of estrogen priming and puberty on the growth hormone response to standardized treadmill exercise and arginine-insulin in normal girls and boys. J Clin Endocrinol Metab 1994; 79:537.
72. Maghnie M, Salati B, Bianchi S, et al. Relationship between the morphological evaluation of the pituitary and the growth hormone (GH) response to GH-releasing hormone Plus arginine in children and adults with congenital hypopituitarism. J Clin Endocrinol Metab 2001; 86:1574.
73. Dietrich RB, Lis LE, Greensite FS, Pitt D. Normal MR appearance of the pituitary gland in the first 2 years of life. AJNR Am J Neuroradiol 1995; 16:1413.
74. Godano E, Morana G, Di Iorgi N, et al. Role of MRI T2-DRIVE in the assessment of pituitary stalk abnormalities without gadolinium in pituitary diseases. Eur J Endocrinol 2018; 178:613.
75. Maghnie M, Strigazzi C, Tinelli C, et al. Growth hormone (GH) deficiency (GHD) of childhood onset: reassessment of GH status and evaluation of the predictive criteria for permanent GHD in young adults. J Clin Endocrinol Metab 1999; 84:1324.
76. David A, Hwa V, Metherell LA, et al. Evidence for a continuum of genetic, phenotypic, and biochemical abnormalities in children with growth hormone insensitivity. Endocr Rev 2011;

32:472.

Topic 5842 Version 35.0

GRAPHICS

Technique for measuring recumbent length



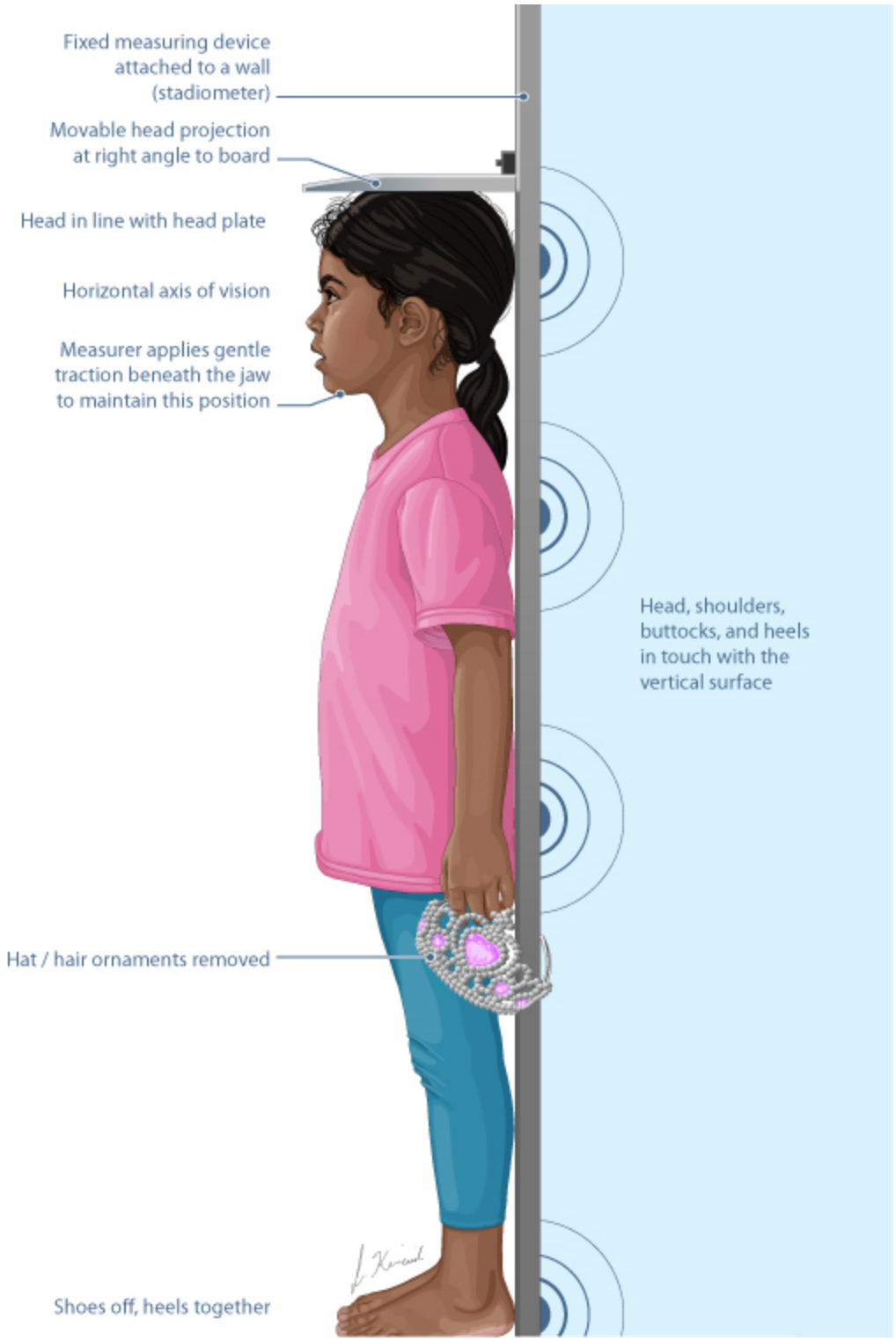
(A) Measurement of length using a length stadiometer. This is the preferred method for measuring stature in a child less than 2 years old. For an accurate measurement, the child must be held fully supine, with knees fully extended, as shown.

(B) Measurement of length using a tape measure. This is less accurate and should only be used if a length stadiometer is not available. The measurement should be done on a firm, flat surface, such as the examining table. With the child held gently in the proper position, make marks on the surface to indicate the position of the head and heels, then remove the child from the table and measure the distance between the marks.

A similar technique may be used for older individuals who are unable to stand, recognizing that recumbent length (when optimally measured) is generally slightly more than standing height.

Graphic 132742 Version 3.0

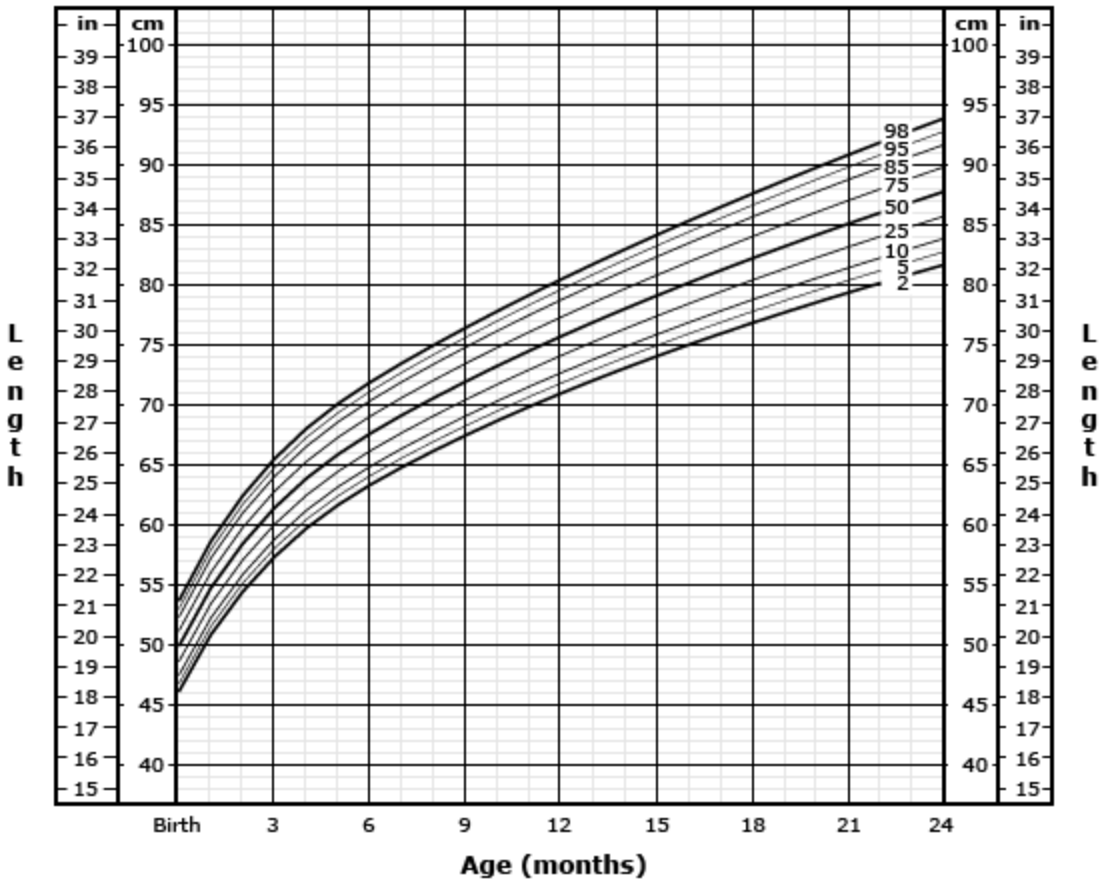
Technique for measuring standing height



The child's shoes and any hats or hair ornaments are removed. The child faces away from the wall with the heels together and the back as straight as possible. The head, shoulders, buttocks, and heels should be in contact with the vertical surface. With the child looking straight ahead, the head projection is placed at the crown of the head. The child steps away from the wall, and the height measurement is recorded to the nearest 0.1 cm.

Graphic 56127 Version 2.0

Length-for-age percentiles, males 0 to 24 months, WHO growth standards

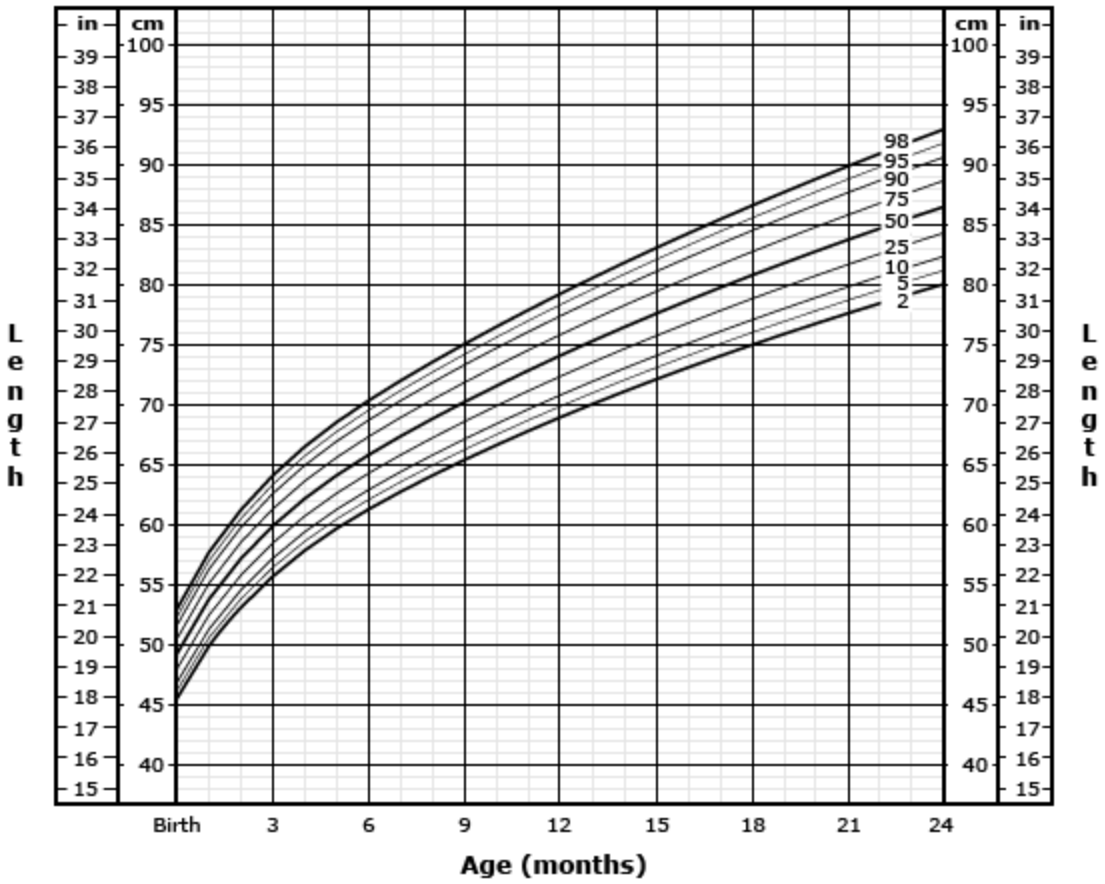


WHO: World Health Organization.

Reproduced from: Centers for Disease Control and Prevention based on data from the WHO Child Growth Standards.

Graphic 67950 Version 6.0

Length-for-age percentiles, females 0 to 24 months, WHO growth standards

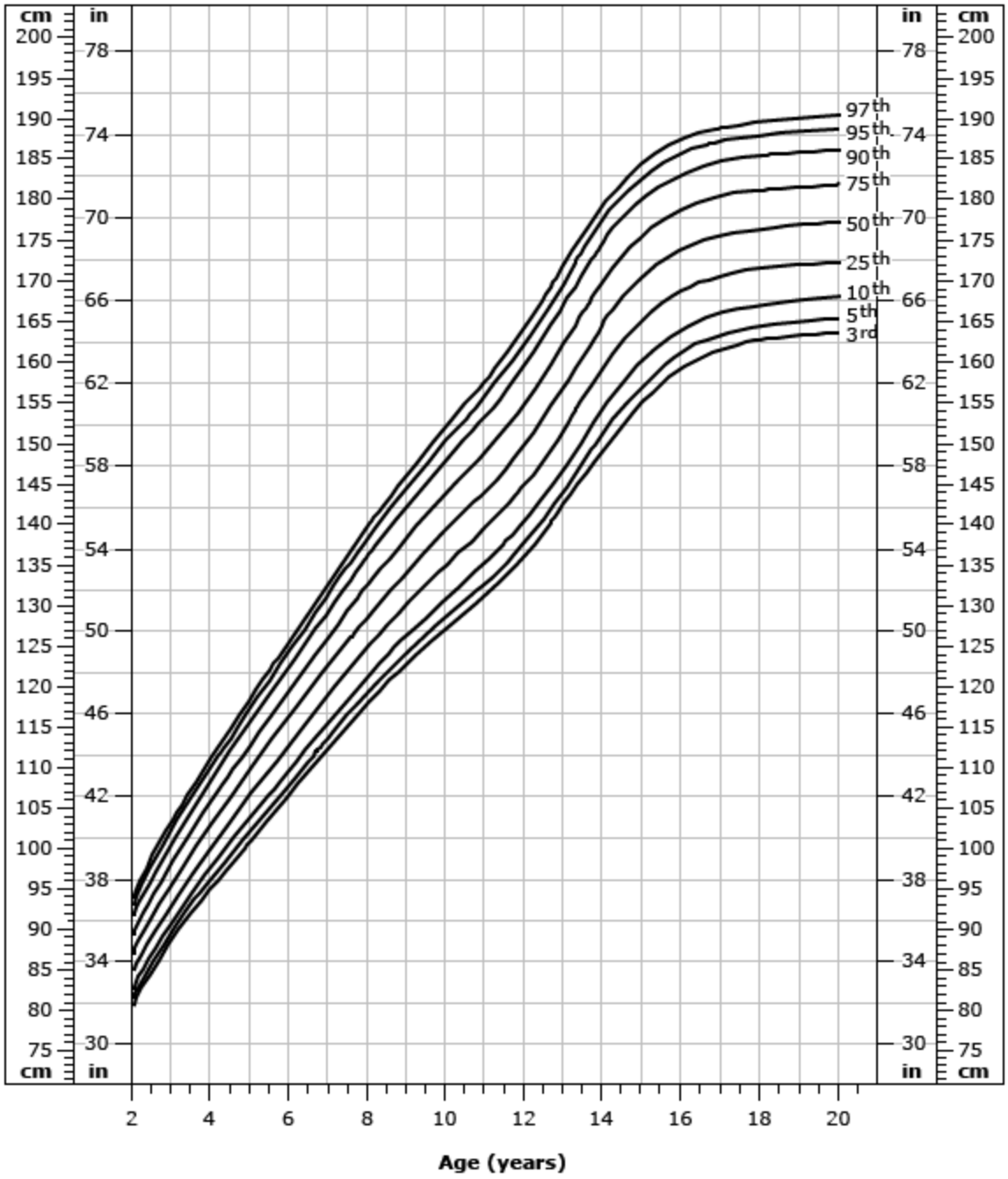


WHO: World Health Organization.

Reproduced from: Centers for Disease Control and Prevention based on data from the WHO Child Growth Standards.

Graphic 80511 Version 4.0

Stature-for-age percentiles, males 2 to 20 years, CDC growth charts: United States

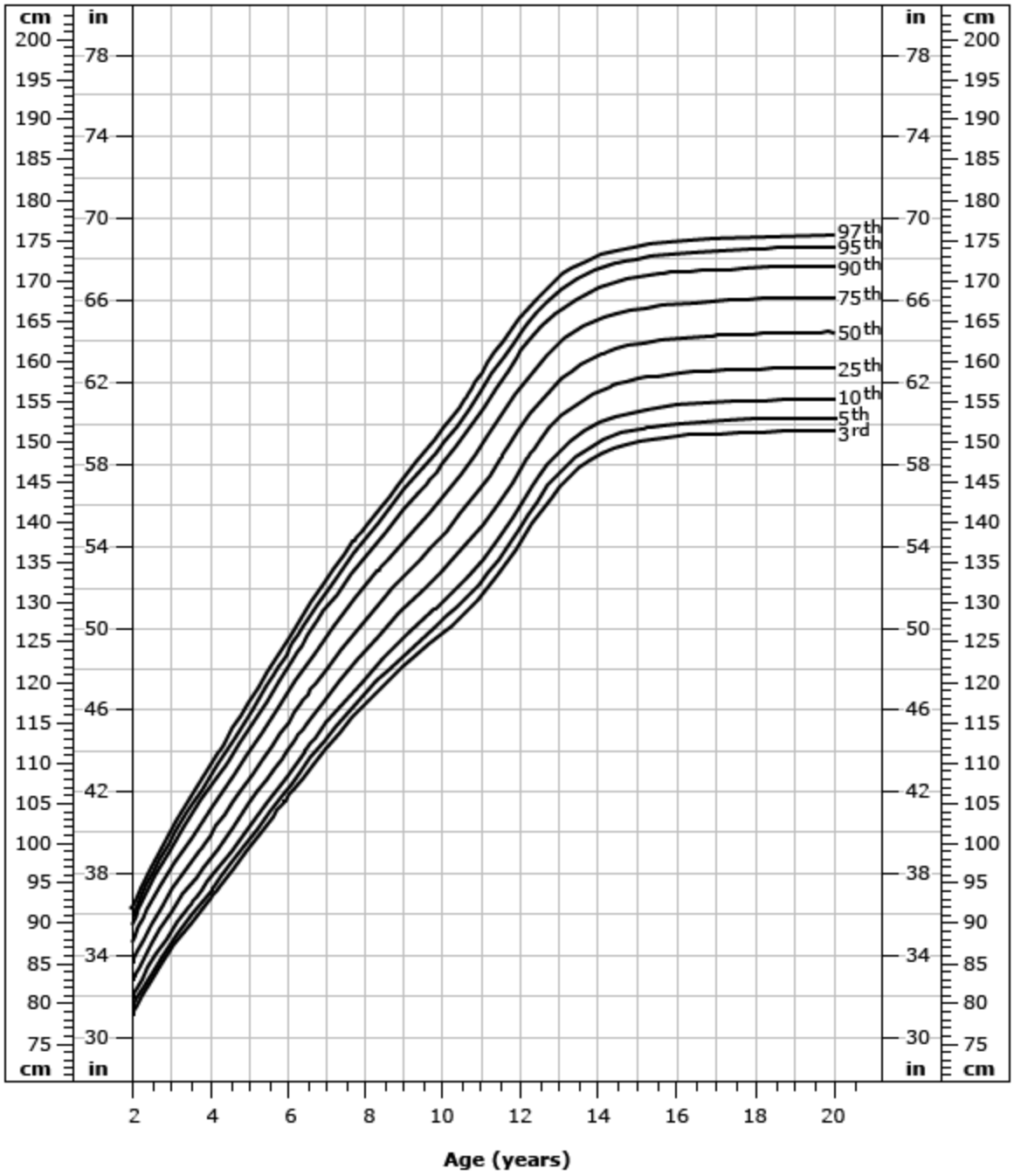


CDC: Centers for Disease Control and Prevention.

From: National Health Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).

Graphic 63399 Version 8.0

Stature-for-age percentiles, females 2 to 20 years, CDC growth charts: United States

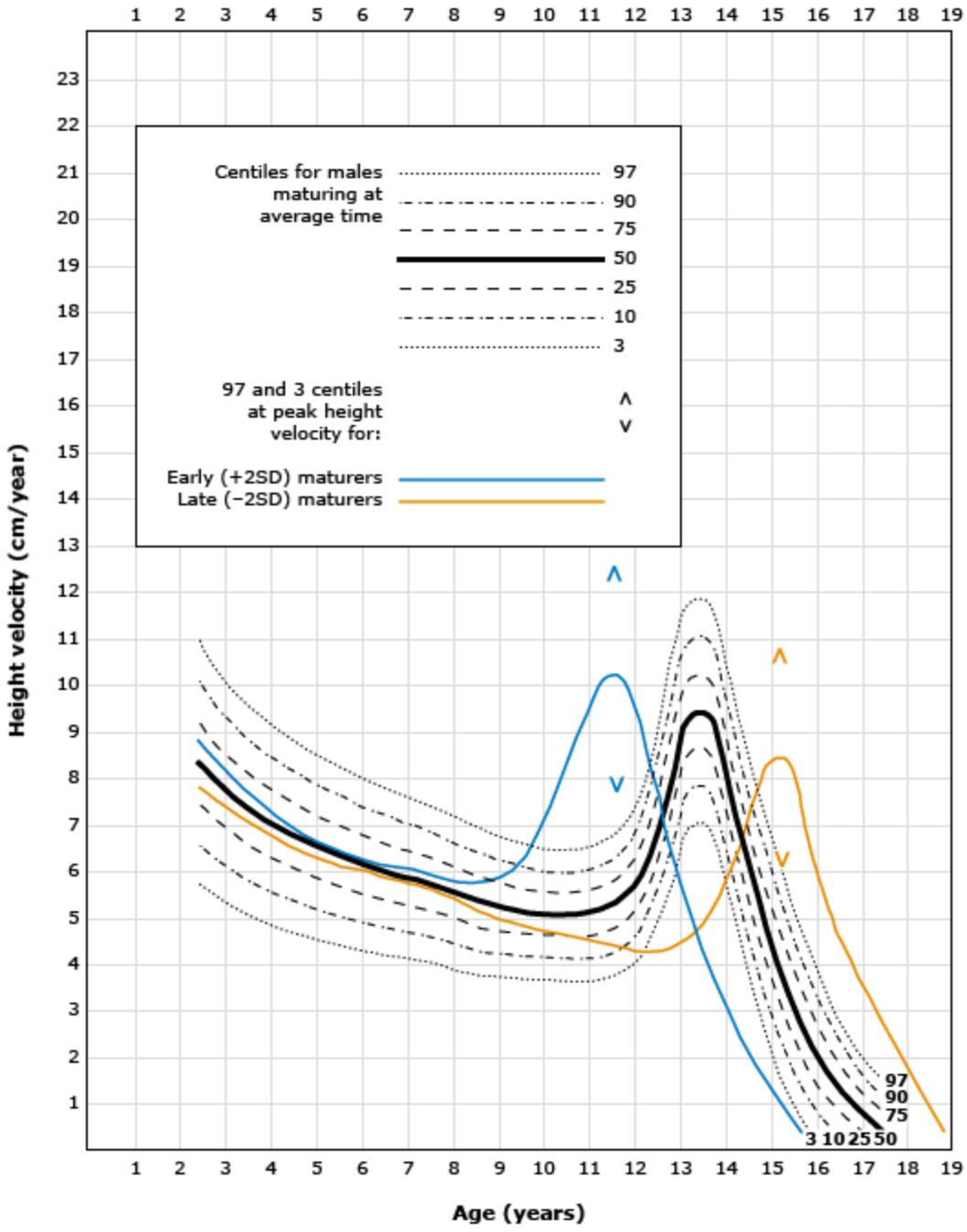


CDC: Centers for Disease Control and Prevention.

From: National Health Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).

Graphic 77249 Version 7.0

Height velocity in American males 2 to 19 years



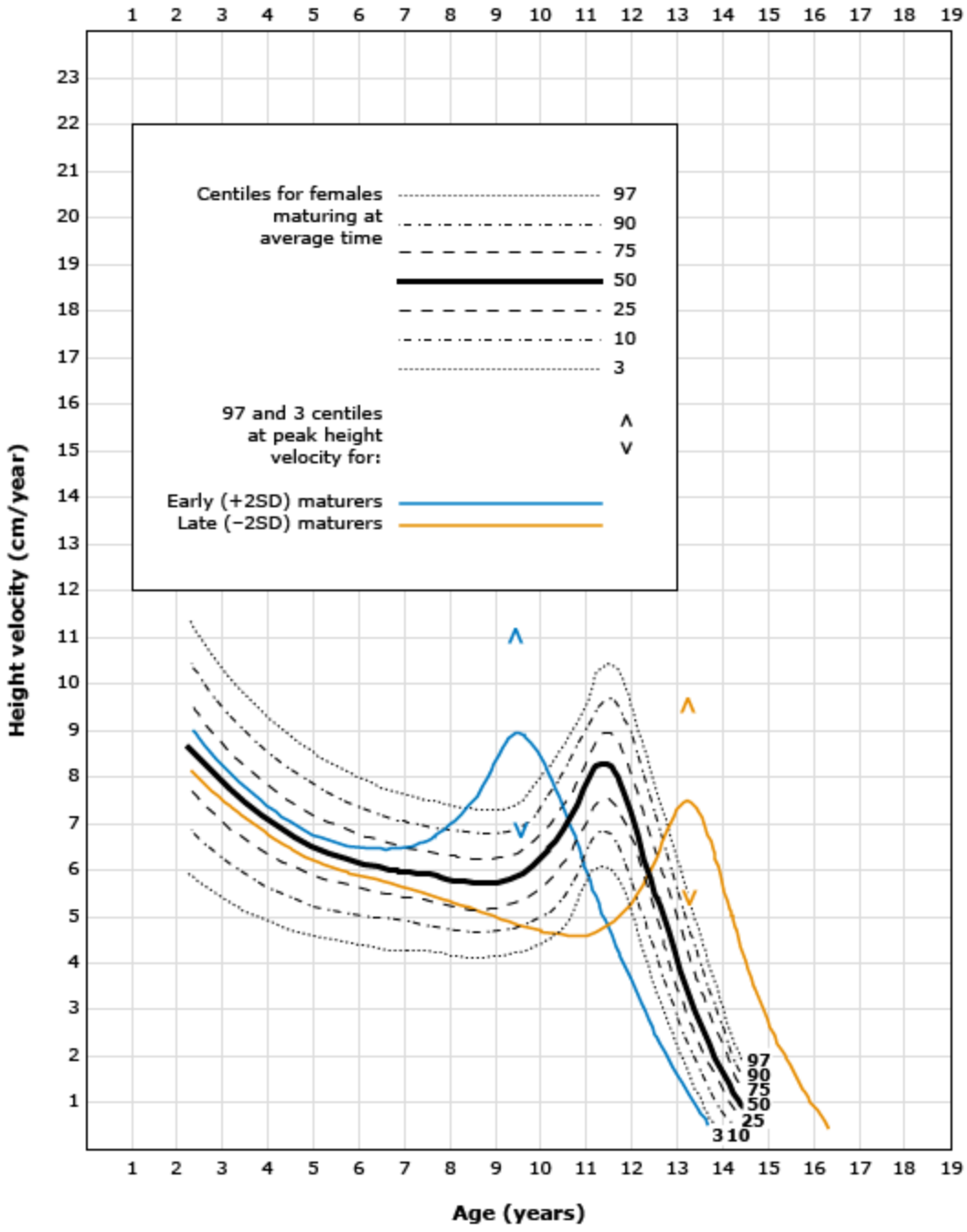
- Height velocity by age for American males. The main set of curves (black lines) is centered on the population with average timing of peak growth velocity (around 13.5 years for males) and show an approximate trajectory for individual children with this average pubertal timing. The 2 other curves outline a trajectory (50th percentile) for a child with "early" (solid blue) or "late" (solid orange) timing of peak growth velocity.
- Other height velocity curves have been developed that reflect population averages (eg, Kelly A, JCEM 2014, not shown here). Those curves are substantially flatter than the trajectory followed by any individual patient. They are based on data from a more recent and ethnically diverse population of

children and are valuable for understanding overall growth patterns in the population but are less appropriate for evaluation of the growth of an individual patient.

SD: standard deviations.

Graphic 96367 Version 9.0

Height velocity in American females 2 to 19 years



- Height velocity by age for American females. The main set of curves (black lines) is centered on the population with average timing of peak growth velocity (around 11.5 years for females) and show an approximate trajectory for individual children with this average pubertal timing. The 2 other curves outline a trajectory (50th percentile) for a child with "early" (solid blue) or "late" (solid orange) timing of peak growth velocity.
- Other height velocity curves have been developed that reflect population averages (eg, Kelly A, JCEM 2014, not shown here). Those curves are substantially flatter than the trajectory followed by any individual patient. They are based on data from a more recent and ethnically diverse population of

children and are valuable for understanding overall growth patterns in the population but are less appropriate for evaluation of the growth of an individual patient.

SD: standard deviations.

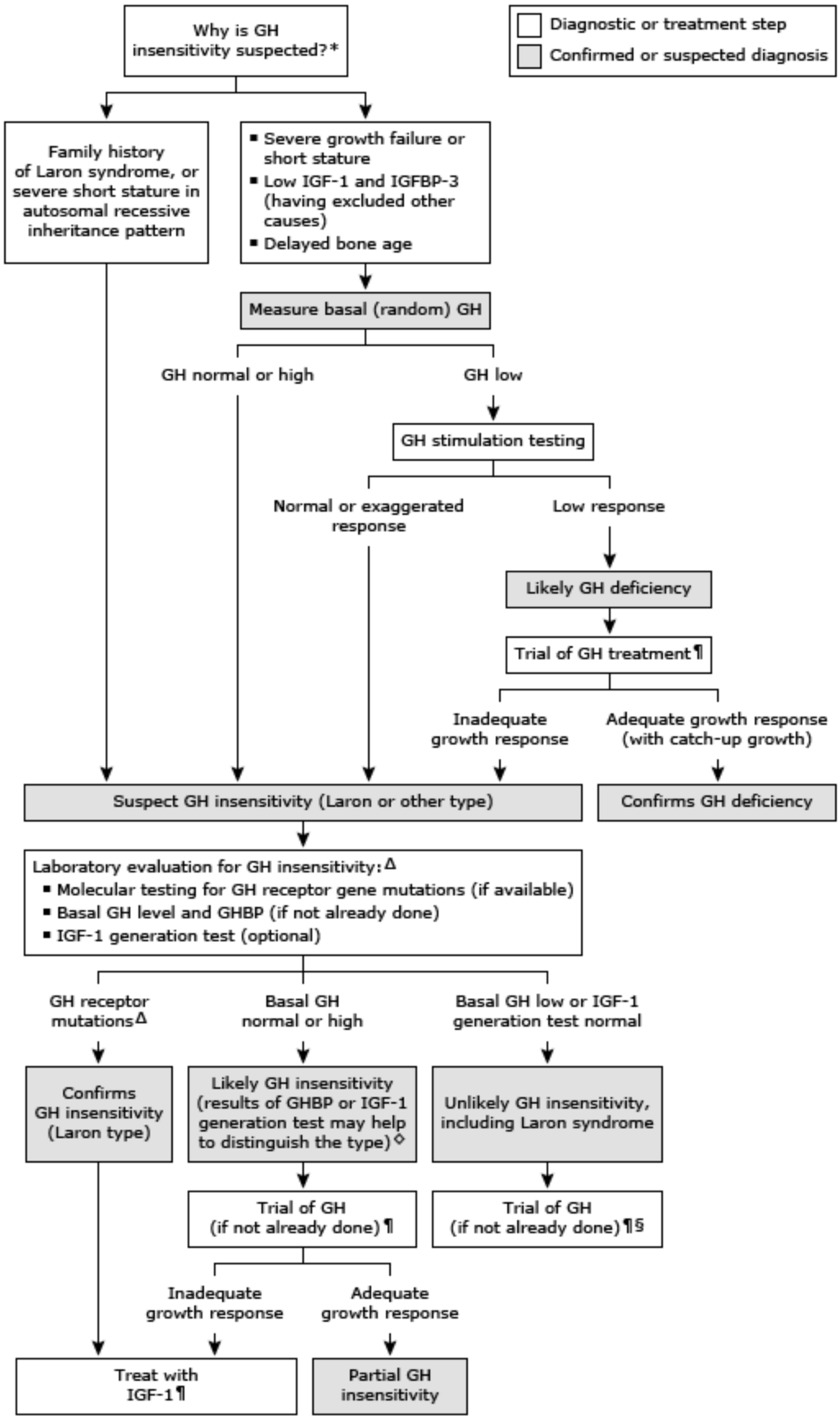
Graphic 96366 Version 8.0

Limitations of provocative testing for growth hormone deficiency in children

Pharmacologic testing is not physiologic
Normality is arbitrarily defined, if defined at all
Reproducibility in both normal and abnormal children is poor, even when the same test is performed
Age and sex steroid hormone status affect the response
Nutritional adequacy and body composition (particularly, adiposity) can affect response
There is no standard serum growth hormone assay, and there are large interassay variations among the assays in use
All of the tests are costly

Graphic 51347 Version 3.0

Evaluation for suspected growth hormone insensitivity in a child



GH: growth hormone; IGF-1: insulin-like growth factor 1; IGFBP-3: insulin-like growth factor-binding protein 3; GHBP: growth hormone-binding protein.

* Refer to UpToDate topic reviews on the diagnostic approach to short stature and diagnosis of GH deficiency in children.

¶ Trials of GH or IGF-1 should be performed only if the epiphyses are open. An adequate growth response is an increase in height velocity by at least 2.5 cm/year. Children whose epiphyses are nearly closed may not achieve this degree of growth response, even if they have GH deficiency or insensitivity.

Δ In a patient with suspected GH insensitivity, the possibility of Laron syndrome can be assessed by molecular testing for pathogenic homozygous or compound heterozygous mutations in the GH receptor gene. Laron syndrome is the most common form of severe GH insensitivity. Alternatively, the possibility of GH insensivity can be supported by measuring basal GH levels and GHBP or performing an IGF-1 generation test (IGF-1 response to a brief trial of recombinant GH). The results of the IGF-1 generation test are not always useful, because the protocols for performing this test have not been standardized and the levels of IGF-1 achieved are quite variable.

◇ In patients with clinical characteristics of severe GH insensitivity and a normal or elevated circulating GH level, a low level of GHBP strongly supports a diagnosis of Laron syndrome, but normal levels are uninformative. This is because patients with Laron syndrome have low GHBP levels only if the GH receptor mutation affects the extracellular binding domain, whereas GHBP levels are normal or high if the GH receptor mutation affects the transmembrane or cytoplasmic domain of the GH receptor.

§ Adequate growth response to GH confirms GH deficiency. If the growth response is inadequate, consider the possibility of an IGF-1 receptor mutation.

Graphic 112625 Version 3.0

Contributor Disclosures

Erick J Richmond Padilla, MD Speaker's Bureau: Merck [Growth hormone]; NovoNordisk [Growth hormone]; Pfizer [Growth hormone]; Sandoz [Growth hormone]. All of the relevant financial relationships listed have been mitigated. **Alan D Rogol, MD, PhD** Consultant/Advisory Boards: Ascendis [Growth]; BioMarin [Growth]; Comprehensive Drug Testing [Anti-doping]; Lumos [Growth]; Pfizer [Growth]; Tolmar [Growth and androgens]; United States Anti-Doping Agency [Anti-doping]; World Anti-Doping Agency [Anti-doping]. All of the relevant financial relationships listed have been mitigated. **Mitchell E Geffner, MD** Grant/Research/Clinical Trial Support: Adrenas [Congenital adrenal hyperplasia]; Diurnal [Congenital adrenal hyperplasia]; Neurocrine Biosciences [Congenital adrenal hyperplasia]; Novo Nordisk [Growth]; Spruce Biosciences [Congenital adrenal hyperplasia]. Consultant/Advisory Boards: Adrenas [Congenital adrenal hyperplasia]; Aeterna Zentaris [Growth]; Eton [Congenital adrenal hyperplasia]; Neurocrine Biosciences [Congenital adrenal hyperplasia]; Novo Nordisk [Growth]; Pfizer [Growth]; Spruce Biosciences [Congenital adrenal hyperplasia]. Speaker's Bureau: Eton [Congenital adrenal hyperplasia]. Other Financial Interest: McGraw-Hill textbook royalties [Pediatric endocrinology]. All of the relevant financial relationships listed have been mitigated. **Jessica Kremen** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

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