Consensus Statement on the Diagnosis and Treatment of Children with Idiopathic Short Stature: A Summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop

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Objective: Our objective was to summarize important advances in the management of children with idiopathic short stature (ISS).

Participants: Participants were 32 invited leaders in the field.

Evidence: Evidence was obtained by extensive literature review and from clinical experience.

Consensus: Participants reviewed discussion summaries, voted, and reached a majority decision on each document section.

Conclusions: ISS is defined auxologically by a height below −2 SD score (SDS) without findings of disease as evident by a complete evaluation by a pediatric endocrinologist including stimulated GH levels. Magnetic resonance imaging is not necessary in patients with ISS. ISS may be a risk factor for psychosocial problems, but true psychopathology is rare. In the United States and seven other countries, the regulatory authorities approved GH treatment (at doses up to 53 μg/kg·d) for children shorter than −2.25 SDS, whereas in other countries, lower cutoffs are proposed. Aromatase inhibition increases predicted adult height in males with ISS, but adult-height data are not available. Psychological counseling is worthwhile to consider instead of or as an adjunct to hormone treatment. The predicted height may be inaccurate and is not an absolute criterion for GH treatment decisions. The shorter the child, the more consideration should be given to GH. Successful first-year response to GH treatment includes an increase in height SDS of more than 0.3–0.5. The mean increase in adult height in children with ISS attributable to GH therapy (average duration of 4–7 yr) is 3.5–7.5 cm. Responses are highly variable. IGF-I levels may be helpful in assessing compliance and GH sensitivity; levels that are consistently elevated (>2.5 SDS) should prompt consideration of GH dose reduction. GH therapy for children with ISS has a similar safety profile to other GH indications. **(*J Clin Endocrinol Metab* 93: 4210–4217, 2008)**

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Abbreviations: CDGP, Constitutional delay of growth and puberty; GnRHa, GnRH analog; ISS, idiopathic short stature; SDS, SD score.

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Short stature is one of the most common concerns presenting to pediatric endocrinologists and other physicians caring for children. A variety of disease states must be considered and ruled out in children presenting with severe short stature, yet a large number of such children remain without a definitive diagnosis and are labeled as having idiopathic short stature (ISS). The Growth Hormone Research Society together with the Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology agreed upon the organization of an international workshop in 2006 and convened it on October 17–20, 2007, in Santa Monica, CA, to review and weigh available evidence related to the evaluation and management of children with ISS. Leading experts in the field, including representatives of all international pediatric endocrine societies were invited to participate in creating a consensus document on the topic. Industry supporters of the Growth Hormone Research Society were invited to send representatives to the meeting. These individuals participated in all discussions leading to the development of the consensus document and attended sessions presenting the consensus statements but did not participate in the writings of, or vote on, the statements. The workshop participants identified and addressed key issues employing a previously defined model used to achieve consensus statements for the diagnosis and management of adult and pediatric GH deficiency (GHD) (1–3) and produced this comprehensive statement that integrates clinical practice recommendations for the approach to children with ISS. Two discussion documents were prepared by the organizing committee (without industry involvement) before the workshop, one on the evaluation and the other on the management of children with ISS. These two review papers are published separately (4, 5), and the reader is invited to review them for further details. The workshop followed a rigorous structure of breakout group discussion and review of key issues. A writing group transcribed the group reports and discussion summaries into a consensus draft that was carefully and critically reviewed by all participants in a plenary forum on the last day. Participants (except industry delegates) voted and reached a majority decision on each section of the document. They were sent a polished draft for additional comments and gave signed approval to the final revision.

Definition and Epidemiology

ISS is defined as a condition in which the height of an individual is more than 2 SD score (SDS) below the corresponding mean height for a given age, sex, and population group without evidence of systemic, endocrine, nutritional, or chromosomal abnormalities (6). Specifically, children with ISS have normal birth weight and are GH sufficient. ISS describes a heterogeneous group of children consisting of many presently unidentified causes of short stature. It is estimated that approximately 60–80% of all short children at or below −2 SDS fit the definition of ISS (7). This definition of ISS includes short children labeled with constitutional delay of growth and puberty (CDGP) and familial short stature. The frequency of referral of these children is dependent on the socioeconomic environment; furthermore, there is a greater perceived disability of short stature in boys compared with girls, irrespective of social class. Children with dysmorphic phenotypes, such as skeletal dysplasias or Turner syndrome, and those with birth weight or length that are small for gestational age should be excluded from the ISS diagnostic category as are children with clearly identified causes of short stature (*e.g.* celiac disease, inflammatory bowel disease, juvenile chronic arthritis, GHD or GH resistance, hypothyroidism, Cushing's syndrome, *etc.*).

Subcategorization

ISS should be subcategorized, principally based on auxological criteria. The main distinction is between children with a familial history of short stature, whose heights are within the expected range for parental target height and those children who are short for their parents. Although the midparental height is commonly calculated by the Tanner method (average of the father's and mother's height plus or minus 6.5 cm), a more accurate estimate can be achieved using a corrected target height SDS, which is calculated as $0.72 \times$ average of father's and mother's height SDS and the lower limit of the target height range as corrected target height minus 1.6 SDS (8). It is generally accepted that, on average, adult height achieved in children with ISS is below the parental target height (9).

ISS should also be classified by the presence or absence of bone age delay, indicating the probability of delayed growth and puberty. Subcategorization may help to predict adult height, which would be expected to be greater in a child with delayed maturation. Short individuals with no family history of short stature generally have a lower adult height in comparison with target height.

Evaluation of the Short Child

The evaluation of the short child always begins with a careful medical history, including family and past medical history, and a comprehensive physical examination, including phenotypic characteristics, body proportions, and pubertal staging. Specific attention should be paid to the possibility of consanguinity and the timing of puberty in the parents as well as the stature of first- and second-degree relatives. Birth history should be reviewed for abnormalities of fetal growth and perinatal complications and information collected pertaining to past illness or symptoms of chronic disease, medication use, nutritional status, and psychosocial and cognitive development. The child's and the parents' perceptions of the problem as well as their levels of concern should be assessed. Every effort should be made to obtain and plot all previous growth measurements on the appropriate chart (10). For evaluation of children less than 5 yr of age, the World Health Organization recommends the use of their recently published growth curves (11). For the assessment of older children, the use of ethnic-specific growth charts, where available, is preferred. For children adopted from developing countries, specific charts from the country of origin are advised for the first gen-

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eration. After that, charts specific to the adopting country seem more appropriate. The physical exam should begin with quantification of the degree of growth failure and proportionality using arm span, sitting height or upper-to-lower segment ratios, body mass index, and for children under 4 yr of age, measurement of the head circumference. Dysmorphic features, which may indicate a syndromic diagnosis, should be sought, as should signs of chronic illness or endocrinopathy.

Screening Tests and Initial Diagnostic Testing

In patients for whom the history and physical exam do not suggest a particular diagnosis, screening laboratory tests are indicated. These include a complete blood count, erythrocyte sedimentation rate, creatinine, electrolytes, bicarbonate, calcium, phosphate, alkaline phosphatase, albumin, TSH, and free T_4 and IGF-I levels. Screening for celiac disease is also recommended. A karyotype should be performed in all girls with unexplained short stature, and in short boys with associated genital abnormalities. A bone age x-ray should be obtained and reviewed by an expert. This gives an indication of the child's remaining growth potential and may narrow the differential diagnosis. A skeletal survey should be reserved for patients with suspicion of a skeletal dysplasia, such as those with abnormal body proportions or a height SDS substantially below midparental height SDS and should be read by an expert in bone disorders.

Investigation of the GH-IGF Axis

GHD must be excluded to make a diagnosis of ISS. This requires both clinical and biochemical evaluation, because no single test or set of tests can define GHD. GH testing should be performed in any patient with a compatible history and physical examination or a low height velocity or in whom low IGF-I levels are observed. The majority of experts concur that a patient who is short, with normal height velocity, no bone age delay, and a plasma IGF-I level above the mean for age does not require GH testing. A minority recommended pursuing GH testing irrespective of IGF-I concentration. The choice of GH stimuli to be used is highly country dependent, as is the decision to prime with sex steroids. In a child with clinical criteria for GHD, a peak GH concentration less than 10 ng/ml has traditionally been used to support the diagnosis. At the present time, a new GH reference standard is being introduced that may require a downward adjustment of the lower limit of normal. In addition, changes in assay methodology influence choice of cutoff values for the diagnosis of GHD. Measures of spontaneous GH secretion (nocturnal or 24-h profiles) are not indicated for routine assessment of GH status. In contrast, it is strongly recommended that IGF-I levels be obtained as part of the evaluation. IGFBP-3 measurements add little to the evaluation of short stature except in children younger than 3 yr, where low IGFBP-3 levels are helpful in the diagnosis of GHD (12). Reliable assay performance and appropriate normative data are critical for successful use of GH and IGF-I measurements in clinical practice. It is acknowledged that there is a wide variability in GH and IGF-I values and in their interpretation among currently available commercial and in-house assays. This reflects diverse assay methodology as well as the adequacy and applicability of normative data. In the evaluation of a short child, a hypothalamic-pituitary magnetic resonance imaging is performed in children with confirmed GHD or if an intracranial lesion is suspected. If a diagnosis of ISS is made, magnetic resonance imaging is not indicated. Although it is clear that there is variable GH sensitivity among children with short stature, the IGF-I generation test, although capable of documenting severe GH insensitivity, cannot currently detect more moderate degrees. Attempts should be made to improve diagnostic utility by generating better normative data. A search for alternative indices of GH sensitivity should be encouraged.

Genetic Tests

In situations where a specific genetic diagnosis associated with short stature is expected (such as Noonan syndrome or GH insensitivity syndrome), the genes of interest should be examined. Online resources exist such as Genetest (www.genetests.org), which identify laboratories capable of performing these tests. Although routine analysis of SHOX should not be undertaken in all children with ISS, SHOX gene analysis should be considered for any patient with clinical findings compatible with SHOX haploinsufficiency (13).

Psychosocial Consequences of ISS

With currently available data, it is difficult to generalize on the impact of short stature on psychosocial adaptation. Short stature may be a risk factor for psychosocial problems, such as social immaturity, infantilization, low self-esteem, and being bullied, especially for those referred for evaluation. The large interindividual differences in adaptation to short stature and on the impact of being short may be a function of several risk and protective factors, including parental attitudes and prevailing cultural opinions (14). Stress experiences may be frequent, but true psychopathology is rare (15). Overall, both clinical and population studies indicate that most short individuals are functioning within the broad range of normalcy; however, it is of note that extremely short children (<-2.5 SDS) have not been adequately studied.

Ethical Principles in the Management of Children with ISS

The diagnosis and treatment of children with ISS should be under the auspices of pediatric endocrinologists, and management decisions should be evidence based. The interest of the child is the primary concern. One must discourage the expectation that taller stature is necessarily associated with positive changes in quality of life. Growth-promoting measures should be effective and should take into consideration the risks, benefits, and treat-

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ment alternatives including counseling. Treatment must include continuous and ongoing evaluation of efficacy and safety as well as the option of changing the therapy, the dosing strategy, or discontinuation of therapy, when the growth response is poor, when an acceptable height is attained, or if the youth withdraws assent for treatment. The primary goal of treatment is attainment of a normal adult height. A desired secondary goal is reaching a normal height during childhood. Physicians are responsible for engaging families in discussion that must involve an honest and realistic appraisal of treatment expectations for height gain and the variability of clinical outcome (16).

Criteria for Treating Children with ISS

Auxological

The height criteria for consideration of therapy vary based on geographical and clinical parameters. In the United States and seven other countries, the regulatory authorities have approved GH treatment for children shorter than −2.25 SDS (1.2 percentile). Among this working consensus group, opinions regarding the appropriate height below which GH treatment could be considered ranged from −2 to −3 SDS. Age should be taken into account when deciding to initiate treatment. It is felt that the optimal age for initiating treatment is 5 yr to early puberty; most studies on the GH therapy of children with ISS examined children older than 3–4 yr.

Biochemical

There are no accepted biochemical criteria for initiating GH treatment in ISS.

Psychological

The clinician should weigh the degree of short stature and the coping capacity of the child. Therapy would generally not be recommended for the short child who is unconcerned about his/her stature; alternatively, the clinician may be more likely to consider medical or psychological intervention for the child who seems to suffer from his/her shortness. The psychological benefits of GH therapy in such children have yet to be proven (14). However, robust measures to prove the psychological value of GH therapy in such children remain elusive, at least in part because of the recognized limitations in quantitating outcomes (17).

The Role of GH Treatment Alternatives

Anabolic steroids

Oxandrolone has been shown to increase height velocity in the short term in several controlled studies but does not significantly increase predicted or measured adult height. Low-dose testosterone therapy causes short-term acceleration of linear growth with minimal or no advancement of bone age or decrease in adult height potential. Although both of these drugs are useful in males with CDGP with mild to moderate short stature (>−2.5 SDS) (18), testosterone is the most appropriate treatment for boys with CDGP with an adult height prediction within the normal range. Oxandrolone offers the advantage of oral administration, but the disadvantages of being weakly androgenic and carrying the remote risk of hepatotoxicity.

IGF-I

In the United States, Japan, and Europe, IGF-I is approved for short stature with severe IGF deficiency associated with normal GH secretion (or GH insensitivity) (19).

In ISS children who do not respond to GH treatment, IGF-I therapy is a theoretical option; however, data are lacking regarding efficacy and safety in this population.

GnRH analogs (GnRHa)

Monotherapy with GnRHa in both sexes has shown a small and variable effect on adult height gain and is generally not recommended. Concerns have been raised regarding potential adverse effects of GnRHa, including on short-term bone mineral density (20) and on the psychological consequences of delaying puberty (21). Combination therapy with GnRHa and GH, however, has potential value if the GnRHa is used for at least 3 yr.

Aromatase inhibitors

Aromatase inhibition may facilitate growth in the presence of androgens, whereas bone age advancement is slowed due to inhibition of estrogen production. An increase in predicted adult height has been shown in males with ISS (22), but adult height data are not available. There is insufficient evidence for its use in females with ISS. The long-term efficacy and safety of aromatase inhibitors in males with ISS has not been demonstrated. The results of ongoing studies on combined treatment with GH and aromatase inhibitors show that combination treatment for at least 2 yr slows down the tempo of bone age acceleration and increases predicted adult height (23). Long-term follow-up of these patients is still required.

Psychological counseling

Psychosocial interventions to support the adaptation process to short stature and to enhance personal resources for coping with stress experiences as well as social action to reduce prejudices are worthwhile to consider instead of or as an adjunct to hormone treatment (14). No data have been reported about the effect of such interventions.

Are There Specific Therapies for Various Patient Subtypes?

In children with CDGP, whose puberty and bone age are substantially delayed and who are taller than −2.5 height SDS, testosterone is the appropriate therapy in boys, where this clinical picture is far more prevalent than in girls. In late-maturing girls, low-dose estrogens represent a theoretical option; however, there are no published data to support its use. In ISS children where CDGP is unlikely, GH therapy could be considered.

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The Role of Predicted Adult Height in the Decision to Treat with GH

The predicted adult height may be inaccurate in individuals but can be helpful together with other criteria (family pubertal history and midparental target height) in deciding to treat with GH. In a longitudinal study of ISS subjects, bone age delay had an impact on the accuracy of prediction. In children with a bone age delay around 2 yr, the average adult height was close to the predicted height, and in those with no bone age delay, adult height surpassed the initial prediction substantially, although if the bone age was delayed by more than 2 yr, adult height was considerably below predicted height (24).

The Role of Current Height in the Decision to Treat with GH

The shorter the child, the more consideration should be given to treatment with GH. The U.S. Food and Drug Administration (FDA)-approved cutoff in the United States (and seven other nations) is −2.25 SDS, whereas in other countries lower cutoffs are proposed. Children whose heights are below −2.0 SDS and who are more than 2.0 SDS below their midparental target height and/or have a predicted height below −2.0 SDS are also believed by some experts to warrant treatment consideration.

Defining the Response to GH Treatment

Short-term auxological features that suggest a successful first-year response to GH treatment in individual patients include a change in height SDS of more than 0.3–0.5, a first-year height velocity increment of more than 3 cm/yr, or a height velocity SDS of more than +1. Restoration to a more normal height during childhood is an important consideration. Mathematical models can be used to estimate responses to therapy with the selected dose (25).

Biochemical features

Serial IGF-I measurements during GH therapy are useful to assess efficacy, safety, and compliance and have been proposed as a tool for adjusting the GH dose. No other biochemical tests are routinely recommended in GH-treated ISS patients.

Psychological features

An important rationale for treatment with GH is the assumption that it will improve quality of life. Validated instruments sensitive to the specific domains that are affected in short children and that are easily administered in the clinic are needed but are not currently recommended as part of routine care.

Interpretation of Outcome Measures Assessing the Success of GH Treatment

Short-term outcome measures (*i.e.* <2 yr) must take into account the age, pubertal status, and degree of growth retardation of the individual patient. In most children with ISS, the change in height SDS will provide the best indicator of response, but height velocity, height velocity SDS, and the change in height velocity (centimeters per year or SDS) all have utility, and are sometimes superior, in assessing response when interpreted in light of the patient's clinical situation. Long-term auxological parameters that define the success of therapy include adult height SDS, adult height SDS minus height SDS at start of GH, adult height minus predicted height, and adult height minus target height. Long-term psychosocial and metabolic outcomes should be evaluated in registries for these patients.

Outcome of GH Therapy in Children with ISS

The mean increase in adult height attributable to GH therapy (average duration of 4–7 yr) in children with ISS is 3.5–7.5 cm compared with historical controls (26, 27), with patients' own pretreatment predicted adult heights (28), or with nontreatment control or placebo control groups (29, 30).

Responses are highly variable and are dose dependent. Concern has been raised that higher GH doses (>53 μg/kg·d) may advance the bone age and the onset of puberty (31), but this has not been found in other studies (32).

Multiple factors affect the growth response to GH, many of which are unknown. Children who are younger or heavier, who receive higher GH doses, and who are shortest relative to target height have the best growth response. These factors account for approximately 40% of the variance in growth response. Adult height outcome is influenced negatively by age at start and positively by midparental height, height at start, bone age delay, and the first-year response to GH (23, 24). The utility of baseline and treatment-related biochemical data including IGF-I has not been validated in long-term studies, but 2-yr studies suggest that the rise in IGF-I correlates with short-term height gain (30).

Monitoring for Efficacy and Safety in GH-Treated Children with ISS

Children treated with GH should be monitored for height, weight, pubertal development, and adverse effects at 3- to 6-month intervals. Regular monitoring for scoliosis, tonsillar hypertrophy, papilledema, and slipped capital femoral epiphysis should be performed as part of the regular physical exam during follow-up visits. We recommend that after 1 yr, the response to therapy be assessed by calculating height velocity SDS as well as the change in height SDS. Pubertal stage should be assessed regularly, and bone age may be obtained periodically to reassess height prediction and for consideration of intervention to modify the tempo of puberty. IGF-I levels may be helpful in guiding GH dose adjustment, but the significance of abnormally elevated IGF-I levels remains unknown. Thus far, no instances of elevated blood glucose in GH-treated patients with ISS have been reported, but there is controversy regarding the need for routine monitoring of glucose metabolism.

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GH Treatment Adjustment Strategies

Dosage is usually selected and adjusted by weight. If the growth response is considered inadequate, the dose may be increased. There are no definitive data concerning the long-term safety of doses higher than 50 μg/kg·d in children with ISS. The upper limit of GH dosage used in other pediatric conditions is approximately 70 μg/kg·d (28, 33), but the possibility of using such doses varies in terms of national health economics. In the United States, the current FDA-approved doses for GH in ISS are up to 0.3–0.37 mg/kg · wk (34). In the future, growth prediction models may improve GH dosing strategies. IGF-I levels may be helpful in assessing compliance and GH sensitivity; levels that are consistently elevated (>2.5 SDS) should prompt consideration of GH dose reduction. Recent studies on IGF-based dose adjustments in ISS demonstrated increased short-term growth when higher IGF targets were selected, but this strategy has not been validated in long-term studies with respect to safety, cost effectiveness, or adult height (31).

Consideration of Adding Puberty Modulators

If height prediction is below −2.0 SDS at the time of pubertal onset in either sex, the addition of GnRHa may be considered as discussed above (35, 36). Alternatively, in males, aromatase inhibitors may be an option (22). However, long-term efficacy and safety data are not available for either of these interventions. Also, the impact of delayed puberty on somatic and psychological development is not known. We do not recommend aromatase inhibitors for girls.

Duration of GH Treatment

There are two schools of thought about the duration of treatment. One is that treatment should stop when near adult height is achieved (height velocity <2 cm/yr and/or bone age >16 yr in boys and >14 yr in girls). Alternatively, therapy can be discontinued when height is in the normal adult range (above −2 SDS) or has reached another cutoff for the reference adult population (for example, in Australia, the 10th percentile; elsewhere, the 50th percentile). Stopping therapy is influenced by patient/family satisfaction with the result of therapy or ongoing cost-benefit analysis or when the child wants to stop for other reasons.

Possible GH Side Effects

The possible side effects in GH-treated children with ISS are similar to those previously reported in children receiving GH therapy for other indications (37). However, the frequency of adverse events is generally less (38). No long-term adverse effects have been documented. Posttreatment surveillance with focus on cancer prevalence and metabolic side effects is recommended, but the feasibility of such studies is unclear.

Cost/Benefit Analysis

The average ultimate height gain attributable to GH treatment in children with ISS, as well as the cost, are known (10,000–20,000 dollars/cm), but the short- and long-term benefits for the individual and society are unclear (26). It is presently not known whether, and how, a gain in height relates to change in quality of life. Therefore, GH treatment for children with ISS should be put in the context of the health budget for the specific country. At the current time, data demonstrating improved quality of life, better psychological health, *etc.* have not yet been collected in well-controlled studies. Therefore, recommendations for treatment that increases adult height should be balanced with the high cost of these therapies.

The Definition of GH Nonresponsiveness

The expected result of GH treatment in ISS is an increase in height SDS and height velocity resulting in increased adult height. Because there is a continuum of GH responses, the definition of nonresponsiveness is arbitrary. Suggested criteria for poor first-year response include height velocity SDS less than +1 or change in height SDS less than 0.3–0.5, depending on age. Emerging tools for the definition of GH treatment failures include prediction modeling and age- and gender-specific growth-response charts (39). If the growth response is lower and compliance is assured, among the options considered may be increasing the dose of GH. IGF-I values can be used to assess compliance and sensitivity to GH. If after 1–2 yr and higher doses of GH, the growth rate is still inadequate, GH treatment should be stopped and alternative therapies could be entertained.

Future Studies

Future studies on the management of children with ISS should involve three major areas. The first is improvement in diagnostic tools to categorize the different subpopulations who fall within the definition of ISS and their response to therapy. These would include molecular genetics, proteomics, and pharmacogenomics, better measures of GH and IGF-I sensitivity, and improved prediction models. The second area should involve psychosocial instruments, interventions, and outcomes. A third area is the conduct of well-controlled studies on the use of adjunctive pharmacological interventions such as the combination of GH and GnRHa, aromatase inhibitors, or IGF-I.

Conclusions

ISS represents a significant clinical entity within the pediatric endocrinology practice, and multiple therapeutic interventions may be considered for these patients after appropriate evaluation has been conducted. Further clinical research and development is warranted to optimize the management of these children and to ensure that treatments are safe and beneficial.

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References

1. 1998 Consensus guidelines for the diagnosis and treatment of adults with growth hormone deficiency: summary statement of the Growth Hormone Research Society Workshop on Adult Growth Hormone Deficiency. J Clin Endocrinol Metab 83:379–381
2. 2000 Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. J Clin Endocrinol Metab 85:3990–3993
3. **Ho KK, 2007 GH Deficiency Consensus Workshop Participants** 2007 Consensus guidelines for the diagnosis and treatment of adults with growth hormone deficiency. II. A summary statement of the Growth Hormone Research Society in association with the European Society for Pediatric Endocrinology, the Lawson Wilkins Society, the European Society for Endocrinology, the Japan Endocrine Society and the Endocrine Society of Australia. Eur J Endocrinol 157:695–700
4. **Wit JM, Clayton PE, Rogol AD, Savage MO, Saenger PH, Cohen P** 2008 Idiopathic short stature: definition, epidemiology, and diagnostic evaluation. Growth Horm IGF Res 18:89–110
5. **Wit JM, Reiter EO, Ross JL, Saenger PH, Savage MO, Rogol AD, Cohen P** 2008 Idiopathic short stature: management and growth hormone treatment. Growth Horm IGF Res 18:111–135
6. **Ranke MB** 1996 Towards a consensus on the definition of idiopathic short stature. Horm Res 45(Suppl 2):64–66
7. **Lindsay R, Feldkamp M, Harris D, Robertson J, Rallison M** 1994 Utah Growth Study: growth standards and the prevalence of growth hormone deficiency. J Pediatr 125:29–35
8. **Hermanussen M, Cole J** 2003 The calculation of target height reconsidered. Horm Res 59:180–183
9. **Luo ZC, Albertsson-Wikland K, Karlberg J** 1998 Target height as predicted by parental heights in a population-based study. Pediatr Res 44:563–571
10. **Centers for Disease Control** 2000 CDC growth charts: United States. http://www.cdc.gov/growthcharts/
11. **World Health Organization** 2008 The WHO child growth standards. http://www.who.int/childgrowth/en/
12. **Cianfarani S, Liguori A, Boemi S, Maghnie M, Iughetti L, Wasniewska M, Street ME, Zucchini S, Aimaretti G, Germani D** 2005 Inaccuracy of insulin-like growth factor (IGF) binding protein (IGFBP)-3 assessment in the diagnosis of growth hormone (GH) deficiency from childhood to young adulthood: association to low GH dependency of IGF-II and presence of circulating IGFBP-3 18-kilodalton fragment. J Clin Endocrinol Metab 90:6028–6034
13. **Rappold G, Blum WF, Shavrikova EP, Crowe BJ, Roeth R, Quigley CA, Ross JL, Niesler B** 2007 Genotypes and phenotypes in children with short stature: clinical indicators of SHOX haploinsufficiency. J Med Genet 44:306–313
14. **Visser-van Balen H, Geenen R, Kamp GA, Huisman J, Wit JM, Sinnema G** 2007 Long-term psychosocial consequences of hormone treatment for short stature. Acta Paediatr 96:715–719
15. **Sandberg DE, Colsman M** 2005 Growth hormone treatment of short stature: status of the quality of life rationale. Horm Res 63:275–283
16. **Allen DB, Fost NC** 2004 Growth hormone for short stature: ethical issues raised by expanded access. J Pediatr 144:648–652
17. **Ross JL, Sandberg DE, Rose SR, Leschek EW, Baron J, Chipman JJ, Cassorla FG, Quigley CA, Crowe BJ, Roberts K, Cutler Jr GB** 2004 Psychological adaptation in children with idiopathic short stature treated with growth hormone or placebo. J Clin Endocrinol Metab 89:4873–4878
18. **De Luca F, Argente J, Cavallo L, Crowne E, Delemarre-Van de Waal HA, De Sanctis C, Di Maio S, Norjavaara E, Oostdijk W, Severi F, Tonini G, Trifiro G, Voorhoeve PG, Wu F** 2001 International Workshop on Management of Puberty for Optimum Auxological Results. Management of puberty in constitutional delay of growth and puberty. J Pediatr Endocrinol Metab 14(Suppl 2):953–957
19. **Chernausek SD, Backeljauw PF, Frane J, Kuntze J, Underwood LE, GH Insensitivity Syndrome Collaborative Group** 2007 Long-term treatment with recombinant insulin-like growth factor (IGF)-I in children with severe IGF-I deficiency due to growth hormone insensitivity. J Clin Endocrinol Metab 92: 902–910
20. **Yanovski JA, Rose SR, Municchi G, Pescovitz OH, Hill SC, Cassorla FG, Cutler Jr GB** 2003 Treatment with a luteinizing hormone-releasing hormone agonist in adolescents with short stature. N Engl J Med 348:908–917
21. **Mazur T, Clopper RR** 1991 Pubertal disorders: psychology and clinical management. Endocrinol Metab Clin North Am 20:211–227
22. **Hero M, Wickman S, Dunkel L** 2006 Treatment with the aromatase inhibitor letrozole during adolescence increases near-final height in boys with constitutional delay of puberty. Clin Endocrinol (Oxf) 64:510–513
23. **Mauras N, Gonzalez de Pijem L, Hsiang HY, Desrosiers P, Rapaport, R,**

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Schwartz ID, Klein KO, Singh RJ, Miyamoto A, Bishop K 2008 Anastrozole increases predicted adult height of short adolescent males treated with growth hormone: a randomized, double-blind, placebo-controlled multicenter trial for one to three years. J Clin Endocrinol Metab 93:823–831

24. **Wit JM, Rekers-Mombarg LT** 2002 Dutch Growth Hormone Advisory Group. Final height gain by GH therapy in children with idiopathic short stature is dose dependent. J Clin Endocrinol Metab 87:604–611
25. **Ranke MB, Lindberg A, Price DA, Darendeliler F, Albertsson-Wikland K, Wilton P, Reiter EO**2007 KIGS International Board. Age at growth hormone therapy start and first-year responsiveness to growth hormone are major determinants of height outcome in idiopathic short stature. Horm Res 68:53–62
26. **Bryant J, Baxter L, Cave CB, Milne R** 2007 Recombinant growth hormone for idiopathic short stature in children and adolescents. Cochrane Database Syst Rev Jul 18:CD004440
27. **Hintz RL, Attie KM, Baptista J, Roche A** 1999 Effect of growth hormone treatment on adult height of children with idiopathic short stature. Genentech Collaborative Group. N Engl J Med 340:502–507
28. **Wit JM, Rekers-Mombarg LT, Cutler GB, Crowe B, Beck TJ, Roberts K, Gill A, Chaussain JL, Frisch H, Yturriaga R, Attanasio AF** 2005 Growth hormone (GH) treatment to final height in children with idiopathic short stature: evidence for a dose effect. J Pediatr 146:45–53
29. **Finkelstein BS, Imperiale TF, Speroff T, Marrero U, Radcliffe DJ, Cuttler L** 2002 Effect of growth hormone therapy on height in children with idiopathic short stature: a meta-analysis. Arch Pediatr Adolesc Med 156:230–240
30. **Leschek EW, Rose SR, Yanovski JA, Troendle JF, Quigley CA, Chipman JJ, Crowe BJ, Ross JL, Cassorla FG, Blum WF, Cutler Jr GB, Baron J, National Institute of Child Health and Human Development-Eli Lilly, Co. Growth Hormone Collaborative Group** 2004 Effect of growth hormone treatment on adult height in peripubertal children with idiopathic short stature: a randomized, double-blind, placebo-controlled trial. J Clin Endocrinol Metab 89:3140–3148
31. **Kamp GA, Waelkens JJ, de Muinck Keizer-Schrama SM, Delemarre-Van de Waal HA, Verhoeven-Wind L, Zwinderman AH, Wit JM** 2002 High dose growth hormone treatment induces acceleration of skeletal maturation and an earlier onset of puberty in children with idiopathic short stature. Arch Dis Child 87:215–220
32. **Cohen P, Rogol AD, Howard CP, Bright GM, Kappelgaard AM, Rosenfeld RG, American Norditropin Study Group** 2007 Insulin growth factor-based dosing of growth hormone therapy in children: a randomized, controlled study. J Clin Endocrinol Metab 92:2480–2486
33. **Clayton PE, Cianfarani S, Czernichow P, Johannsson G, Rapaport R, Rogol A** 2007 Management of the child born small for gestational age through to adulthood: a consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society. J Clin Endocrinol Metab 92:804–810
34. **US Food and Drug Administration** www.fda.gov/medwatch/SAFETY/2003/03Jul_PI/Humatrope_PI.pdf
35. **Tanaka T** 2007 Sufficiently long-term treatment with combined growth hormone and gonadotropin-releasing hormone analogue can improve adult height in short children with isolated growth hormone deficiency (GHD) and non-GHD short children. Pediatr Endocr Rev 5:471–481
36. **van Gool SA, Kamp GA, Visser-van Balen H, Mul D, Waelkens JJ, Jansen M, Verhoeven-Wind L, Delemarre-van de Waal HA, de Muinck Keizer-Schrama SM, Leusink G, Roos JC, Wit JM** 2007 Final height outcome after three years of growth hormone and gonadotropin-releasing hormone agonist treatment in short adolescents with relatively early puberty. J Clin Endocrinol Metab 92:1402–1408
37. **Tanaka T, Cohen P, E Clayton P, Laron Z, L Hintz R, C Sizonenko P** 2002 Diagnosis and management of growth hormone deficiency in childhood and adolescence. Part 2. Growth hormone treatment in growth hormone deficient children. Growth Horm IGF Res 12:323–341
38. **Quigley CA, Gill AM, Crowe BJ, Robling K, Chipman JJ, Rose SR, Ross JL, Cassorla FG, Wolka AM, Wit JM, Rekers-Mombarg LT, Cutler Jr GB** 2005 Safety of growth hormone treatment in pediatric patients with idiopathic short stature. J Clin Endocrinol Metab 90:5188–5196
39. **Bakker B, Frane J, Anhalt H, Lippe B, Rosenfeld RG** 2008 Height velocity targets from the national cooperative growth study for first-year growth hormone responses in short children. J Clin Endocrinol Metab 93:352–357

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