Clinical Practice Committee Publication

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

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Abstract

Background/Aims: On behalf of the Drug and Therapeutics, and Ethics Committees of the Pediatric Endocrine Society, we sought to update the guidelines published in 2003 on the use of growth hormone (GH). Because idiopathic short stature (ISS) remains a controversial indication, and diagnostic challenges often blur the distinction between ISS, GH deficiency (GHD), and primary IGF-I deficiency (PIGFD), we fo- cused on these three diagnoses, thereby adding recombi- nant IGF-I therapy to the GH guidelines for the first time. ***Methods:*** This guideline was developed following the GRADE approach (Grading of Recommendations, Assess- ment, Development, and Evaluation). ***Results:*** This guideline provides recommendations for the clinical management of children and adolescents with growth failure from GHD, ISS, or PIGFD using the best available evidence. ***Conclusion:*** The taskforce suggests that the recommendations be applied in clinical practice with consideration of the evolving literature and the risks and benefits to each individual patient. In many instances, careful review highlights areas that need further research.

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In the decade since the publication of the last guidelines for the use of growth hormone (GH) by the Drug and Therapeutics Committee of the Pediatric Endocrine Society (PES; formerly named in honor of Lawson Wilkins) [1], both the field and the approach to guidelines have changed considerably. This report serves to update the 2003 guidelines by following the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group [2]. The large number of approved indications for GH treatment is too unwieldy to review in this manner in a single document. Because idiopathic short stature (ISS) remains a controversial indication, and diagnostic challenges often blur the distinction between ISS, GH deficiency (GHD), and primary IGF-I deficiency (PIGFD), we focused on these three diagnoses in this guidelines statement. Thus, we have added recombinant IGF-I therapy to the GH guidelines for the first time.

In 1985, GHD became the first indication for recombinant human GH approved by the US Food and Drug Administration (FDA), which it described as "the treatment of pediatric patients who have growth failure due to inadequate secretion of endogenous GH." In 2003, the FDA expanded GH use to the treatment of ISS, also called non-GH-deficient short stature, defined by height standard deviation score (SDS) ≤–2.25 (≤1.2nd percentile) and associated with growth rates unlikely to permit attainment of adult height (AH) in the normal range, in pediatric patients for whom diagnostic evaluation excludes other causes of short stature that should be observed or treated by other means. The height cutoff of –2.25 SD (1.2nd percentile) corresponds in adults to 160 cm (63 inches) for men and 150 cm (59 inches) for women [3]. The FDA approved IGF-I treatment in 2005 for the long-term treatment of growth failure in pediatric patients with severe PIGFD (defined as both height and serum IGF-I concentration below –3 SD despite normal or elevated GH levels) or with GH gene deletion who developed neutralizing antibodies to GH after a trial of GH therapy. The FDA further stipulated that IGF-I is not indicated to treat secondary IGF-I deficiency resulting from GHD, malnutrition, hypothyroidism or other causes; thus, it is not a substitute for GH therapy. The definitions have evolved since the original FDA indications, with the most recent iteration provided by the International Classification of Pediatric Endocrine Diagnoses (ICPED) [4].

These guidelines provide recommendations for the clinical management of children and adolescents with growth failure due to GHD, ISS, or PIGFD by systemati-cally reviewing the published evidence regarding various practices. In many instances, careful review revealed a paucity of evidence and highlighted areas that need further research. The lack of studies of sufficient quality in support of a practice is not the same as evidence against the practice; until such studies can be performed, individualization of clinical care remains the central tenet of therapy.

Summary of Recommendations

1. Efficacy of GH Treatment for GHD

1.1. We recommend the use of GH to normalize AH and avoid extreme shortness in children and adolescents with GHD. (Strong recommendation, ●●●●)

1.2. We suggest against routine cardiac testing, dual X-ray absorptiometry (DXA) scanning, and measurement of lipid profiles in children and adolescents treated with GH. (Conditional recommendation, ●●○○)

2. Consideration and Diagnosis of GHD

2.1. Conditions where GH provocative testing is not required to diagnose GHD.

Of note, for patients who do not meet the following criteria yet present a high index of suspicion, GHD can be diagnosed by the conventional approach.

2.1.1. We suggest establishing a diagnosis of GHD without GH provocative testing in patients possessing all of the following three conditions: auxological criteria, hypothalamic-pituitary defect (such as major congenital malformation [ectopic posterior pituitary and pituitary hypoplasia with abnormal stalk], tumor or irradiation), and deficiency of at least one additional pituitary hormone. (Conditional recommendation, ●●○○)

2.1.2. We suggest that GHD due to congenital hypopituitarism be diagnosed without formal GH provocative testing in a newborn with hypoglycemia who does not attain a serum GH concentration above 5 μg/L and has deficiency of at least one additional pituitary hormone and/or the classical imaging triad (ectopic posterior pituitary and pituitary hypoplasia with abnormal stalk). (Conditional recommendation, ●●○○)

Technical Remark: A low GH concentration at the time of spontaneous hypoglycemia is alone insufficient to diagnose GHD.

2.2. GH provocative testing.

2.2.1. We recommend against reliance on GH provocative test results as the sole diagnostic criterion of GHD. (Strong recommendation, ●●●●)

Technical Remark: Very low peak GH levels on provocative testing are consistent with severe GHD, and patients with such results are expected to benefit greatly from GH treatment. However, the threshold test result that distinguishes normal from partial GHD that responds to treatment has not been well established.

Technical Remark: Given the substantial number of healthy, normally growing children who test below accepted limits, inadequate response to two different provocative tests is required for diagnosis of GHD. While it is possible that combining tests might yield different results from tests performed on separate days, there is no evidence against performing both tests sequentially on the same day.

Technical Remark: GH responses to provocative testing are blunted in obese or overweight individuals, and the peak values decrease with increasing body mass index (BMI). Unlike adults, obesity-dependent modifications to diagnostic criteria in children are undetermined.

2.2.2. Given the large discrepancies between GH assays, we recommend that institutions require laboratories to provide harmonized GH assays using the somatropin standard, IRP IS 98/574, 22k rhGH isoform, as recommended by the 2006 and 2011 consensus statements, and the published commutability standards. (Strong recommendation, ●●●●)

2.2.3. We suggest sex steroid priming prior to provocative GH testing in prepubertal boys older than 11 and in prepubertal girls older than 10 years with AH prognosis within –2 SD of the reference population mean in order to prevent unnecessary GH treatment of children with constitutional delay of growth and puberty. (Conditional recommendation, ●●○○)

Technical Remark: Best available evidence exists for boys; evidence is extrapolated to girls.

Technical Remark: A reasonable approach in both boys and girls would be 2 mg (1 mg for body weight <20 kg) of β-estradiol (not ethinyl estradiol) orally on each of the 2 evenings preceding the test. Alternatively, boys can be primed with intramuscular testosterone (50–100 mg of a depot formulation administered 1 week before the test).

Technical Remark: This recommendation applies to GH-naïve patients; it does not retroactively apply to patients already on GH treatment.

2.3. Measurement of spontaneous GH secretion.

2.3.1. We recommend against the use of spontaneous GH secretion in the diagnosis of GHD in a clinical setting. (Strong recommendation, ●●○○)

3. Dosing of GH Treatment for Patients with GHD

3.1. We recommend the use of weight-based or body surface area (BSA)-based GH dosing in children with GHD. (Strong recommendation, ●●●○)

Technical Remark: We cannot make a recommendation regarding IGF-I-based dosing because there are no published AH data using this method. The rationale is logical, but the target IGF-I level has not been established to optimize the balance between AH gain, potential risks, and cost.

3.2. We recommend an *initial* GH dose of 0.16–0.24 mg/kg/week (22–35 μg/kg/day) with individualization of subsequent dosing. (Strong recommendation, ●●○○)

Technical Remark: Some patients may require higher doses.

3.3. We suggest measurement of serum IGF-I levels as a tool to monitor adherence and IGF-I production in response to GH dose changes. We suggest that the GH dose be lowered if serum IGF-I levels rise above the laboratory-defined normal range for the age or pubertal stage of the patient. (Conditional recommendation, ●○○○)

3.4. During puberty, we recommend against the routine increase in GH dose to 0.7 mg/kg/week in every child with GHD. (Strong recommendation, ●●○○)

3.5. We recommend that GH treatment at pediatric doses not continue beyond attainment of a growth velocity below 2–2.5 cm/year. The decision to discontinue pediatric dosing prior to attainment of this growth velocity should be individualized. (Strong recommendation, ●●○○)

4. Safety Issues of GH Treatment for Patients with GHD

4.1. We recommend that prospective recipients of GH treatment receive anticipatory guidance regarding the potential adverse effects of intracranial hypertension, slipped capital femoral epiphysis (SCFE), and scoliosis progression. (Ungraded good practice statement)

4.2. We recommend monitoring of GH recipients for potential development of intracranial hypertension, SCFE, and scoliosis progression by soliciting pertinent history and performing a physical examination at every follow-up clinic visit; further testing should be pursued if indicated. (Strong recommendation, ●●●●)

4.3. We recommend re-assessment of both the adrenal and thyroid axes after initiation of GH therapy in patients whose cause of GHD is associated with possible multiple pituitary hormone deficiencies (MPHD). (Strong recommendation, ●●○○)

Technical Remark: Evaluate for possible central adrenal and thyroid insufficiencies in those not yet diagnosed, and consider increasing hydrocortisone and/or levothyroxine doses in those already on these hormone replacement(s).

4.4. We recommend discussion about and monitoring of glucose metabolism of GH recipients who are at increased risk for diabetes due to insulin resistance. (Ungraded good practice statement)

4.5. Counseling prospective recipients of GH treatment regarding the risk of neoplasia.

4.5.1. We recommend informing at-risk patients about available data and encourage long-term follow-up with their oncologist. (Ungraded good practice statement)

4.5.1.1. For children with acquired GHD due to effects of a primary malignancy:

4.5.1.1.1. We recommend shared decision-making that involves the patient, family, oncologist, and treating endocrinologist. Before initiation of GH treatment, we recommend sharing with families the most recent data about risks, including the potential effect of GH treatment on the timing of second neoplasm occurrence. (Ungraded good practice statement)

4.5.1.1.2. For GH initiation after completion of tumor therapy with no evidence of ongoing tumor, a standard waiting period of 12 months to establish "successful therapy" of the primary lesion is reasonable, but can also be altered depending on individual patient circumstances. (Ungraded good practice statement)

Technical Remark: Although many of the intracranial tumors are not "malignant" (i.e., craniopharyngioma), they have the potential to recur. There are no data to suggest treating them differently than malignant tumors with regard to observation periods before initiating GH treatment.

4.5.1.2. In the rare situation where a child with GHD has an accompanying condition with intrinsic increased risk for malignancy (e.g., neurofibromatosis-1, Down syndrome, Bloom syndrome, Fanconi anemia, Noonan syndrome, and Diamond-Blackfan anemia), we recommend providing counseling regarding the lack of evidence concerning GH effect on malignancy risk in these groups. (Ungraded good practice statement)

4.5.2. For children considered not to be at risk, we recommend that counseling includes information about the unknown long-term (i.e., posttreatment) risks of neoplasia still being studied. (Ungraded good practice statement)

4.6. We recommend that prospective recipients of GH treatment be informed about the uncertainty regarding long-term safety (posttreatment adverse effects in adulthood). (Ungraded good practice statement)

5. Transitional Care after Childhood GH Treatment

5.1. We recommend that patients with multiple (≥3) pituitary hormone deficiencies regardless of etiology, or GHD with a documented causal genetic mutation or specific pituitary/hypothalamic structural defect except ectopic posterior pituitary, be diagnosed with persistent GHD. (Strong recommendation, ●●●○)

5.2. We recommend re-evaluation of the somatotropic axis for persistent GHD in persons with GHD and deficiency of only one additional pituitary hormone, idiopathic isolated GHD (IGHD), IGHD with or without a small pituitary/ectopic posterior pituitary, and in patients after irradiation. (Strong recommendation, ●●●○)

Technical Remark: Testing can be performed after a trial of at least 1 month off GH treatment.

5.2.1. We suggest that measurement of the serum IGF-I concentration be the initial test of the somatotropic axis if re-evaluation of the somatotropic axis is clinically indicated. (Conditional recommendation, ●○○○)

5.2.2. We recommend GH provocative testing to evaluate the function of the somatotropic axis in the transition period if indicated by a low IGF-I level. (Strong recommendation, ●●●○)

5.3. We suggest that GH treatment be offered to individuals with persistent GHD in the transition period. There is evidence of benefit; however, the specifics of the patient population that benefits, the optimal time to reinitiate treatment, and the optimal dose are not clear. (Conditional recommendation, ●●○○)

Technical Remark: The transition period is the time from late puberty to establishment of adult muscle and bone composition, and encompasses attainment of AH.

6. GH Treatment of Patients with ISS

6.1. In the USA, for children who meet FDA criteria, we suggest a shared decision-making approach to pursuing GH treatment for a child with ISS. The decision can be made on a case-by-case basis after assessment of physical and psychological burdens, and discussion of risks and benefits. We recommend against the routine use of GH in every child with height SDS (HtSDS) ≤−2.25. (Conditional recommendation, ●●●○)

Technical Remark: While studies have shown GH treatment increases the mean height of treated cohorts, there is marked interindividual variability in responses, including some individuals who do not respond to treatment.

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6.2. We suggest a follow-up assessment of benefit in HtSDS and psychosocial impact 12 months after GH initiation and dose optimization. (Conditional recommendation, ●●○○)

6.3. Because there is overlap in response between dosing groups, we suggest initiating GH at a dose of 0.24 mg/kg/week, with some patients requiring up to 0.47 mg/kg/week. (Conditional recommendation, ●●○○)

7. IGF-I Treatment of Patients with PIGFD

7.1. We recommend the use of IGF-I therapy to increase height in patients with severe PIGFD. (Strong recommendation, ●●●●)

7.2. Given the absence of a single "best" test that predicts responsiveness to GH treatment, we suggest basing the diagnosis of PIGFD/GH insensitivity syndrome (GHIS) on a combination of factors that fall into 4 stages: (Conditional recommendation, ●●●○)

1 Screening: auxological parameters and low IGF-I concentration
2 Causes of secondary IGF-I deficiency must be excluded, including under-nutrition, hepatic disease, and GHD
3 Circulating levels of GH-binding protein (GHBP): very low or undetectable levels suggest Laron syndrome/GHIS while normal levels are noninformative
4 IGF-I generation test and mutation analyses can be helpful, but have limitations

7.3. We recommend a trial of GH therapy before initiating IGF-I for patients with unexplained IGF-I deficiency. Patients with hormone signaling defects known to be unresponsive to GH treatment can start directly on IGF-I replacement; these include patients with very low or undetectable levels of GHBP and/or proven GH receptor (GHR) gene mutations known to be associated with Laron syndrome/GHIS, GH-neutralizing antibodies, *STAT5b* gene mutations, and *IGF1* gene deletion or mutation. (Strong recommendation, ●●○○)

7.4. We suggest an IGF-I dose of 80–120 µg/kg b.i.d. Similar short-term outcomes were seen with 80 and 120 µg, but published studies had limitations and there is no strong evidence supporting superiority of one dose over the other. (Conditional recommendation, ●●○○)

Technical Remark: Outside of the USA, IGF-I is also used at 150–180 µg/kg once daily.

7.5. We recommend administration of IGF-I 20 min after a carbohydrate-containing meal or snack, and education of patients/families on the symptoms and risk of hypoglycemia associated with IGF-I treatment. (Strong recommendation, ●●●●)

8. General Recommendations

8.1. We recommend that physicians with expertise in managing endocrine disorders in children manage or provide consultation for the evaluation for GHD-ISS-PIGFD and treatment thereof. (Ungraded good practice statement)

8.2. We recommend further study of the unresolved issues highlighted in these guidelines. (Ungraded good practice statement)

Methods

Taskforce Members

The guidelines taskforce was comprised of 7 pediatric endocrinologists from USA and Canada, and a pediatric bioethicist. The PES Board of Directors approved the appointment of each taskforce member following the society's conflict of interest review policy (available from the PES administrative offices) prior to project commencement. Completed conflict disclosure forms are available through Degnon Associates Inc., the management firm for PES. PES provided funding for a 1-day meeting attended by all taskforce members in Washington, DC, in May 2013; PES members (i.e., the endocrinologists) were reimbursed the cost of one night's hotel stay, while the bioethicist was reimbursed for hotel plus travel expenses, and all were provided lunch during the meeting. Most of the work was accomplished via regular conference calls and e-mail. Taskforce members received no other remuneration for their work on the guidelines, from either PES or any commercial entities. A member of the GRADE group served as consultant, via telephone for the 1-day meeting, and throughout the writing process.

Literature Review and Grading of the Evidence

A series of key questions pertaining to the clinical management of patients with GHD-ISS-PIGFD was drafted and revised until approved by the PES Board of Directors. A medical informationalist from the Johns Hopkins School of Medicine was recruited to assist with appropriate search term generation, comprehensive database queries, and reference management. PubMed, Embase, and the Cochrane Library databases were queried using the terms "growth hormone", "insulin-like growth factor-I," their synonyms, and their trade names with the following limits: English language, humans, all child 0–18 years, and published 1985–present. Taskforce members created comprehensive lists of synonymous search terms to capture all studies germane to the key questions. The

query excluded studies of pituitary-derived GH due to their poor external validity for clinicians today. A total of ~15,000 citations were retrieved and a web-based database of the resultant references was generated (RefWorks-COS, Bethesda, MD, USA). Approximately 6,300 citations were specific to GHD or PIGFD.

Each key question was assigned a primary and secondary reviewer, who performed a two-stage review. The primary reviewers sorted the citations collected for their key questions for further inclusion or exclusion by judging the topic relevance according to title and abstract. Abstracts excluded by the primary reviewers were re-reviewed by the secondary reviewers to ensure that all appropriate studies were included. In the second stage, the primary reviewers distilled the study design and results of the full papers into evidence review spreadsheets, including their assessment of the applicability and risk of bias of the individual studies. The secondary reviewers then added comments to the primary reviewers' spreadsheets, independently rating the internal and external validity of each paper. Additional pertinent studies that were found in the bibliographies of the reviewed papers, but had been inadvertently omitted in the database, were pulled and similarly reviewed. ClinicalTrials.gov was also searched for ongoing studies that may have affected consideration of the evidence, and FDA adverse event reports supplemented the safety data.

The 2 reviewers graded the totality of evidence and determined the recommendation for the key question according to the GRADE system [2]. In brief, the quality of the evidence was judged as very low (●○○○), low (●●○○), moderate (●●●○), or high (●●●●), reflecting the reviewers' assessment of the quality of the evidence according to GRADE guidelines. Recommendations were assessed as strong (denoted by "We recommend") or conditional (denoted by "We suggest"). In accordance with GRADE guidelines, strong recommendations reflect confidence that providing such care will afford patients, on balance, more good than harm, while conditional recommendations require more individualized consideration of the risk-benefit assessment for a given patient. On occasion, the taskforce made statements that are marked as "ungraded good practice statements." These are recommendations without direct supporting evidence that are usually noncontestable and are important to include in the guideline to emphasize certain aspects of care such as providing counseling and education to patients [5].

At the in-person taskforce meeting, each primary reviewer presented the recommendation and evidence grade for the key question with a summary of the supporting evidence. Discussion ensued until the taskforce achieved consensus, defined as at least 6 of the 8 members agreeing on the recommendation as strong or weak. Notes were kept of each discussion, such that major dissenting opinion(s) could be included in the guidelines, which were written based on the results of the taskforce meeting. Further deliberation occurred after the attended meeting via phone conferences and email to determine the final recommendations.

Guiding Principles

Prior to review of the published evidence, the taskforce created a set of guiding principles to standardize the approach across individual reviewers that was approved by all reviewers. AH was selected as the primary outcome in considerations of efficacy. In the absence of data on AH, surrogate short-term outcomes such as growth velocity, change in height z-score, or change in predicted height were considered, but did not form the basis of a recommendation. This is because the short-term outcomes are dynamic and do not reliably predict AH for many children; wide individual variability exists within the heterogeneous treatment population, and outcomes such as change in predicted AH vary markedly depending on the methodology used [6]. To compare AH data across studies for GHD, the parameter (AH SDS – midparental height [MPH] SDS) was used or calculated from available data. The formula for MPH SDS calculation varied among studies. Therefore, the MPH SDS reported for each study was used. To compare AH data across studies for ISS, the parameter (AH SDS minus baseline HtSDS) was used because of the heterogeneity of the populations (familial short stature and nonfamilial short stature). (AH SDS – MPH SDS) was not used for ISS, because MPH may not reflect genetic potential if one or both of the parents has an undiagnosed condition. Studies utilizing predicted AH were excluded, because the short-term effect of GH on HtSDS, especially in high doses, may overestimate the effect on AH [7].

The taskforce values and preferences were consistent in that harm prevention was the utmost factor in formulating strength of recommendation. As a result, the guidelines describe a conservative approach to treating patients with GHD-ISS-PIGFD, recommending only those practices with supporting evidence of sufficient quality and that minimize potential risks to patients. Recommenda-

tions in this document were made using the existing literature; future studies may provide evidence that contradict or support the recommendations. Therefore, the taskforce suggests that the recommendations be applied in clinical practice with consideration of the evolving literature and the risks and benefits to each individual patient.

Evidence Supporting Each of the Recommendations

1. Efficacy of GH Treatment for GHD

1.1. We recommend the use of GH to normalize AH and avoid extreme shortness in children and adolescents with GHD. (Strong recommendation, ●●●●)

The primary objectives of GH treatment for patients with GHD are acceleration of growth velocity to promote normalization of growth and stature during childhood and attainment of normal AH appropriate for the child's genetic potential. AH data are available in multiple studies of GH treatment for pediatric GHD including GH postmarketing surveillance registries [8–11], a population-based registry [12], a cancer survivor registry [13], and clinic/hospital-based case series [14–17]. Collectively, more than 4,520 patients were treated to AH with a mean HtSDS of approximately –1.0. Patients were treated for a mean duration of 7 years (range 2–15.4 years) using a mean GH dose of 0.25 mg/kg/week (range 0.14–0.7 mg/kg/week). The difference between AH SDS and MPH SDS, which reflects whether a patient has achieved his or her genetic potential, showed a mean difference of –0.4 SD (–2.8 cm) with a range of –0.2 to –0.6 SD (–1.4 to –4.2 cm). In contrast, AH SDS of individuals with untreated idiopathic IGHD had a mean of –4.7, with a range of –3.9 to –6 SD [18].

Analysis of 1,258 patients with GHD from the Pfizer International Growth Study (KIGS) showed that Caucasian patients with IGHD treated with GH achieved a mean AH SDS of –0.8 in males and –1.0 in females [9]. Patients with MPHD achieved a mean AH of –0.7 in males and –1.1 SD in females. [AH SDS – MPH SDS] were –0.2 for IGHD (males) and –0.5 (females); for MPHD –0.4 (males) and –0.8 (females). The mean GH dose was 0.21 mg/kg/week for IGHD and 0.18 mg/kg/week for MPHD. Variables that correlated with total height increment (ΔHtSDS) on multivariate analysis included midparental target height, height gain in the first year, height at the start of GH treatment, duration of GH treatment, the maximum GH peak on provocative testing, presence or absence of MPHD, and birth weight. The variables with highest positive correlation were the MPH SDS and the first-year growth velocity.

In 2,165 patients with idiopathic IGHD from the French population-based registry [12] with a mean chronological age of 13.2 ± 2 years and a mean bone age of 10.6 ± 2.3 years in boys and a mean chronological age of 11.6 ± 1.9 years and a mean bone age of 9.5 ± 2 years in girls, mean height gain was 1.1 ± 0.9 SDS resulting in an average AH of –1.6 SD (girls 154 ± 5 cm and boys 165 ± 6 cm). The AH SDS was 0.4 SD lower than MPH SDS, and the GH dose used was only 0.14 mg/kg/week. Baseline variables that predicted favorable height outcome included younger age at start of GH treatment, greater bone age delay, prepubertal status, and severe GHD. In this cohort, 65% were prepubertal at baseline and 48% had peak GH secretion between 7 and 10 μg/L, raising concern that a significant proportion of patients had constitutional delay of growth and puberty. Sex steroid priming was used in only 2% of patients before GH provocative testing. No data on magnetic resonance imaging (MRI) of the brain and pituitary gland were reported.

The available studies are not controlled and differ in their definition of GHD, with various diagnostic threshold peak GH levels, pharmacological agents employed in the GH provocative tests, and GH assays used. Some included patients who may have had underlying ISS instead of GHD. Registries are limited by the fact that the enrolled population is vastly heterogeneous and limited to those patients who consent to enrollment. AH in idiopathic IGHD depends not only on treatment variables (age at initiation of GH treatment, pubertal delay, peak GH level and GH assay used to define GHD, and GH dose), but also on the criteria used to determine AH and consideration of GH termination. Randomized controlled trials (RCT) of GH would have been unethical, as efficacy of treatment in increasing height of patients with GHD had been shown previously with pituitary GH (data not reviewed here).

1.2. We suggest against routine cardiac testing, DXA scanning, and measurement of lipid profiles in children and adolescents treated with GH. (Conditional recommendation, ●●○○)

In addition to increasing linear growth, GH exerts crucial effects on lipid, protein, and glucose metabolism. Adults with GHD have reduced cardiac mass and impaired cardiac performance, unfavorable lipid profiles, increased body fat, reduced fibrinolytic activity, decreased insulin sensitivity, premature atherosclerosis, and impaired glucose tolerance [19–21]. Few studies have examined the effects of GH treatment for GHD in grow-

ing children and adolescents on cardiac function, lipid metabolism, body composition, adipokines, and peripheral inflammatory markers [22, 23].

Short-term studies (5 case-control [22, 23] and 1 uncontrolled [24]) involving approximately 120 children with GHD documented a positive effect of GH treatment on left ventricular mass, but data on cardiac performance measured by echocardiography (fractional shortening and left ventricular ejection fraction) and vascular function (intimal media thickness at common carotid arteries) were inconsistent. In the prospective, uncontrolled study of Shulman et al., [24], 10 prepubertal children (mean age 5.7 ± 2.7 years; 5 IGHD/5 MPHD (7 with abnormal pituitary gland on MRI and 3 idiopathic) had reduced left ventricular mass that significantly increased after 1 year of GH treatment without any changes in cardiac function, findings similar to those reported by Metwalley et al. [25] and Salerno et al. [26, 27]. In the follow-up by Salerno's group, a 2-year prospective case-control study involving 30 prepubertal children with GHD (27 IGHD and 3 MPHD) compared to healthy children matched by age, sex, BSA, and BMI, reduced left ventricular mass normalized after the first year of GH treatment and improvement in left ventricular mass positively correlated with the increase in IGF-I levels [26]. Left ventricular systolic and diastolic function did not change after 2 years of treatment. However, in another study, subtle alterations in left ventricular systolic function were noted [28].

Data on bone density and body composition in children with GHD are generally more consistent. Using DXA, children with untreated GHD showed decreased bone mineral density, decreased lean mass, and increased fat mass, while GH treatment improved these abnormalities in multiple studies [29–31]. In a 6-year prospective study of 59 children with GHD, lumbar spine bone mineral density, total body bone mineral density, and body composition were measured using DXA [31]. Mean lumbar spine and total body bone mineral densities were reduced at diagnosis and normalized after 1 year of GH treatment; percentage of body fat was increased at baseline and normalized within 6 months. The severity of GHD or presence of other pituitary hormone deficiencies (IGHD vs. MPHD) was not associated with bone mineral density at diagnosis or with response to GH therapy. In contrast, a study of 5 years of GH treatment found a significant increase in lumbar spine bone mineral density z-score in 35 children with IGHD, but not in 15 children with MPHD [32]. The cohort of patients with MPHD in the first study predominantly had acquired GHD mainly due to intracerebral tumors while the latter cohort of MPHD patients was mostly due to congenital pituitary abnormalities. Thus, the duration of GHD, presence of gonadotropin deficiency, and/or inadequacy of sex steroid replacement may explain the difference between their findings.

Data on lipid profiles in children with untreated GHD compared to healthy controls and the effect of GH treatment are inconsistent. Most of these studies involved small cohorts of children, between 12 and 158 patients. Some studies reported unhealthy lipid profiles in untreated GHD compared to healthy controls, which improved with GH treatment [22, 25, 33–35]. In contrast, other studies reported normal lipid profiles compared to healthy controls, but GH treatment led to significant reduction in total and LDL cholesterol levels and in atherogenic indices [26, 28, 31, 36].

Differences in results in the above studies can be attributed to the following factors: severity of GHD (severe defined as peak GH level on provocative testing of either <3 or <5 µg/L vs. partial GHD with peak GH level between 5 and 10 µg/L); IGHD versus MPHD; different GH assays used to define GHD (polyclonal radioimmunoassay vs. immunometric assays); different GH dosages used; and different durations of GH treatment.

2. Consideration and Diagnosis of GHD

2.1. Conditions where GH provocative testing is not required to diagnose GHD.

Of note, for patients who do not meet the following criteria yet present a high index of suspicion, GHD can be diagnosed by the conventional approach.

2.1.1. We suggest establishing a diagnosis of GHD without GH provocative testing in patients possessing all of the following three conditions: auxological criteria, hypothalamic-pituitary defect (such as major congenital malformation [ectopic posterior pituitary and pituitary hypoplasia with abnormal stalk], tumor or irradiation), and deficiency of at least one additional pituitary hormone. (Conditional recommendation, ●●○○)

2.1.2. We suggest that GHD due to congenital hypopituitarism be diagnosed without formal GH provocative testing in a newborn with hypoglycemia who does not attain a serum GH concentration above 5 µg/L and has deficiency of at least one additional pituitary hormone and/or the classical imaging triad (ectopic posterior pituitary and pituitary hypoplasia with abnormal stalk). (Conditional recommendation, ●●○○)

Technical Remark: A low GH concentration at the time of spontaneous hypoglycemia is alone insufficient to diagnose GHD.

"Classical" GHD, as described by Lawson Wilkins refers to the complete or near-complete inability to secrete GH, resulting in extremely slow growth velocity and AH many standard deviations below the mean [37]. In classical GHD, GH treatment restores normal growth, with catch-up to a percentile compatible with MPH, including the upper percentiles of adult stature. In the majority of cases, classical GHD is associated with hypothalamic-pituitary abnormalities on imaging [38], MPHD, or a history of insult to the area such as tumor, surgery, and/or cranial irradiation [39]. In observational studies of these children, provocative tests show GH concentrations very distinct from the normal range such that test precision, reproducibility, and assay performance may not be crucial barriers to precise diagnosis. For example, in a study of 63 treated patients with GHD, all 15 with imaging abnormalities achieved a peak GH concentration below 5 μg/L [38]. Additionally, in the Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS), the median peak GH level was 2.7 μg/L for the 1,071 subjects with GHD plus any imaging abnormality [39]. In KIGS (Pfizer International Growth Study Database), mean GH peak was 3.1 μg/L in children with imaging abnormalities (excluding pituitary hypoplasia) versus 4.9 μg/L for pituitary hypoplasia and 6.6 μg/L for idiopathic GHD [40]. These tests were not validated as a basis for intervention in an RCT, but observational studies tend to show that very low peak GH response correlates with dramatic response to GH treatment [41–43].

Normal neonates have relative hypersomatotropism, with random GH levels higher than older children and adults in the first 5–7 days of life [44, 45] and falling in subsequent weeks [46]. Newborns with congenital GHD associated with panhypopituitarism have a greater incidence of hypoglycemia; of 44 patients with congenital GHD, none of the neonates with IGHD had hypoglycemia, while 60–70% of neonates with panhypopituitarism (with or without abnormalities on imaging) experienced hypoglycemia [47]. Neonatal cholestasis with hypoglycemia occurs in panhypopituitarism and improves with replacement of pituitary hormones including GH [48]. A GH level (whether random or associated with spontaneous hypoglycemia) that distinguishes infants with GHD from those with GH sufficiency has not been established definitively. A retrospective study using a validated assay on dried filter-paper blood spots, found that in 314 newborns less than 5 days old, the median GH concentration was 16.4 μg/L with 95% confidence interval of 7–39.4 μg/L. In contrast, 9 newborns with MPHD had GH levels of 5.5 μg/L or less on the same GH assay but samples were collected from these babies between 5 and 28 days of age [44]. Because of GH assay variability, a GH value of ≤5 μg/L in the first week of life in a neonate with deficiency of other pituitary hormones who experiences hypoglycemia is likely sufficient to accurately diagnose GHD. Beyond the first week of life, there are no clear GH threshold levels that discern normal newborns from those with GHD. Beyond the neonatal period, a low GH concentration at the time of hypoglycemia is alone insufficient to diagnose GHD due to low specificity [49]. The challenges in defining normal GH and IGF-I levels in the first 18 months of life are reviewed elsewhere [50].

2.2. GH provocative testing.

2.2.1. We recommend against reliance on GH provocative test results as the sole diagnostic criterion of GHD. (Strong recommendation, ●●●●)

Technical Remark: Very low peak GH levels on provocative testing are consistent with severe GHD, and patients with such results are expected to benefit greatly from GH treatment. However, the threshold test result that distinguishes normal from partial GHD that responds to treatment has not been well established.

Technical Remark: Given the substantial number of healthy, normally growing children who test below accepted limits, inadequate response to two different provocative tests is required for diagnosis of GHD. While it is possible that combining tests might yield different results from tests performed on separate days, there is no evidence against performing both tests sequentially on the same day.

Technical Remark: GH responses to provocative testing are blunted in obese or overweight individuals, and the peak values decrease with increasing BMI. Unlike adults, obesity-dependent modifications to diagnostic criteria in children are undetermined.

Defining growth failure conceptually implies abnormally low growth velocity, while the definition of inadequate GH secretion must be based on more complex evidence. Many cases of GHD are not accompanied by other hypophyseal hormone deficiencies or known hypothalamic-pituitary pathology (idiopathic GHD) and must be diagnosed by measuring GH levels (other GH-related endpoints, e.g. body composition and IGF-I levels, have insufficient sensitivity and specificity to clearly distinguish children with or without GHD). This is further complicated by the pulsatile nature of GH secretion that necessitates the use of provocative (stimulation) testing.

There are no randomized controlled studies to AH that correlate GH provocative testing results with subsequent GH treatment effects on AH. Available evidence is derived from response to treatment in the first few years and consistently shows some predictive value of peaks <10 µg/L on gain in AH SDS [51–53]. However, there is no controlled, evidence-based gold standard for this cutoff, which was adopted for identifying partial cases in the continuum between complete deficiency and normal. By modern immunometric methods and standards, 10 µg/L is just below the mean response obtained to most provocative tests in normally growing children, whose 5th percentile lies below 5 µg/L for most tests [54, 55].

In the absence of evidence from controlled studies, postmarketing surveys might help estimate how levels within this continuum predict response to treatment. Data from KIGS were mathematically modeled from 593 GH-treated prepubertal children diagnosed as having GHD on the basis of a GH response <10 µg/L [56]. Adding peak GH response to a model of auxological parameters increased the percentage of variance explained from 45 to 60%, making it a statistically significant, but rather modest predictor. However, when individual values for the improvement in first-year height velocity prediction attributable to the GH peak were plotted, the prediction came from peak levels <5 µg/L; at this level, the GH peak increased the prediction by as much as 4 cm of growth in the first year. Similar results were shown in 236 prepubertal children enrolled in the NCGS study in the USA [57]. First-year increase in HtSDS (ΔHtSDS) was indistinguishable between children with peak GH responses 5–10 or >10 µg/L, and ΔHtSDS >1.5 SD was seen only with GH peaks <5 µg/L. The specificity of the cutoff of 10 µg/L was estimated at only 25%. In 1,192 children enrolled in the ICGS study in Japan [58] (also industry-sponsored), a larger ΔHtSDS was seen in children with GH peaks <5 µg/L on two tests, compared to those with at least one test with a peak >5 µg/L. AH analyses from the postmarketing studies are not available and would not be meaningful because of a strong bias to continue treatment only in good early responders.

In addition to lack of AH-based evidence supporting a diagnostically meaningful threshold test result, there are several limitations to comparing peak GH responses across provocative tests. We could find no evidence indicating that peak GH values are similar using different provocative agents. Using the same analytical assay to measure peak GH concentrations of 68 normally growing children, Zadik et al. [54] found good agreement between insulin- and arginine-stimulated GH peaks (14.2 ± 6.3 vs. 13.1 ± 6.1 µg/L), but clonidine, another widely used stimulus, gave much higher levels (21.0 ± 10.7 µg/L). In this study of normally growing children, 1 SD below the mean for peak GH value was at or below 10 µg/L, with the 5th percentile being less than half of this cutoff. These results were corroborated in a large, registry-based study of 3,233 cases in France [59], in which correlation coefficients (r) between GH peaks on two tests in the same patient ranged from 0.35 to 0.6, meaning that the r^2 (expressing the fraction of the total variance explained by the fact that the two tests were performed on the same subject) ranged from 12 to 36%. These results also suggested imperfect reproducibility of the same test in the same patient, with the highest correlation, that being for duplicate testing with insulin stimulation, having a coefficient of only 0.72 (r^2 = 52%).

Studies show that GH response to provocative testing depends on BMI and that GH response to stimulation is considerably lower in obese children [60, 61]. In a prospective study of 65 normally growing obese children, spontaneous GH secretion was less than half of reference, and it normalized after weight loss [62]. There is insufficient evidence for establishing BMI-corrected cutoffs for GH provocative testing in children. A retrospective cross-sectional study of glucagon stimulation testing in adults with BMI ≥25 proposed lowering the diagnostic threshold from the standard 3 µg/L (failed by 45% of the 47 healthy adults studied) to 1 µg/L (failed by 6% of healthy controls, 59% of 41 adults with partial pituitary deficiency, and 90% of the 20 adults with total pituitary deficiency studied) [63]. For the obese child with poor growth, other endocrinopathies (e.g., hypothyroidism and hypercortisolism) should be excluded before testing for GHD, as these conditions, if present and untreated, can cause falsely low GH levels upon GH provocative testing.

2.2.2. Given the large discrepancies between GH assays, we recommend that institutions require laboratories to provide harmonized GH assays using the somatropin standard, IRP IS 98/574, 22k rhGH isoform, as recommended by the 2006 and 2011 consensus statements, and the published commutability standards. (Strong recommendation, ●●●●)

Serum GH concentrations are currently measured using a variety of methods against a variety of standards. Normal values were established using polyclonal radioimmunoassays and purified pituitary standards. Currently used immunometric assays with monoclonal antibodies and recombinant standards have higher specificity, but the use of different standards and antibodies with

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specificities for different GH isoforms has resulted in large discrepancies between assays.

Therefore, standardization or, at least, harmonization is required to meaningfully evaluate and compare results. An important first step in harmonization is the adoption of recombinant primary reference material, the most current and widely used of which is IRP IS 98/574, 22k rhGH isoform, as recommended by the 2006 and 2011 consensus statements [64]. If different methods give the same result for the same serum pools, the assays can be considered standardized. If not, harmonization is achieved by documenting sample-independent differences and deriving correction factors to obtain the same values for the same sample, by the use of commutable serum pools as outlined by Ross et al. [65].

Discrepancies among current GH assays lead to diagnostic misclassifications. Using three reference assays (two using the same standard, 88/624), Hauffa et al. [66] re-examined 699 peak samples from GH provocative testing. The mean difference among assays varied from 5.4 to 10.3 mU/L (2.7 to 5.1 µg/L). Assignment to GHD- versus GH-sufficient groups varied substantially among different assays in a subset of 132 subjects who had had standardized insulin and arginine testing, resulting in misclassification of up to 29% of cases. In another study, samples from 47 provocative tests were assayed with four different methods [67]. Discrepancies were found with significant effects on diagnostic outcome. One immunometric assay classified 36% of tests as indicating GHD compared to 15% for the standard radioimmunoassay.

Several countries have sought to standardize or harmonize their GH assays. A systematic, multi-laboratory effort at standardization of assays in Finland between 1998 and 2003 showed considerable improvement in concordance, but even in the last year of the effort, discrepancies persisted [68]. Another harmonization effort in Germany found a 27% misclassification rate before adjusting results by a conversion factor [69]. In Japan, a systematic effort at harmonization using a uniform biosynthetic standard resulted in lowering of the cutoff from 10 to 6 µg/L due largely to the immunometric methods measuring much lower than the original radioimmunoassay [70].

2.2.3. We suggest sex steroid priming prior to provocative GH testing in prepubertal boys older than 11 and in prepubertal girls older than 10 years with AH prognosis within –2 SD of the reference population mean in order to prevent unnecessary GH treatment of children with constitutional delay of growth and puberty. (Conditional recommendation, ●●○○)

Technical Remark: Best available evidence exists for boys; evidence is extrapolated to girls.

Technical Remark: A reasonable approach in both boys and girls would be 2 mg (1 mg for body weight <20 kg) of β-estradiol (not ethinyl estradiol) orally on each of the 2 evenings preceding the test. Alternatively, boys can be primed with intramuscular testosterone (50–100 mg of a depot formulation administered 1 week before the test).

Technical Remark: This recommendation applies to GH-naïve patients; it does not retroactively apply to patients already on GH treatment.

In children with constitutional delay of growth and puberty, the normal decline in prepubertal growth velocity with age (interrupted by the pubertal growth spurt) is prolonged and may lead to frankly abnormal growth velocity [71]. This is accompanied by a reduction in the GH response to provocative stimuli [72], which has led to the supposition that, in prepubertal children of pubertal age, GH testing be preceded by brief treatment with sex steroids.

Sex steroid priming before GH provocative testing in prepubertal children of pubertal age improves diagnostic specificity without compromising the sensitivity of diagnosing severe GHD and can prevent inappropriate GH treatment of children with constitutional delay of growth and puberty. Administration of 1–2 mg of estradiol to 44 children with ISS raised the mean lower 95% confidence interval of peak GH response to a sequential arginine-clonidine test from clearly "abnormal" at 3.7 up to 8.3 µg/L. This very substantial gain in specificity was not accompanied by a loss of sensitivity, as response was unaltered in 15 children with GHD established by the presence of other pituitary defects (7 of the 15 cases), imaging findings, or other phenotypic features [73]. In a longitudinal study of 8 children with delayed puberty, mean peak GH response was 8.2 µg/L, below the GHD cutoff and substantially lower than that seen in control children of prepubertal age. Mean peak response completely normalized to 15.8 µg/L when the children developed puberty 0.83–2.14 years later [72]. Similar results were found in a cross-sectional study of 84 normal, untreated children, where the percentage of those who would have been classified as GHD by the stricter cutoff of 7 µg/L declined from 61% at Tanner stage I to zero at stages IV and V [74]. An observational study reported AH in 50 otherwise healthy boys evaluated for short stature with delayed puberty (mean delay of 2 years) and growth velocity <5 cm/year. These boys had peak GH values in the deficient range without sex steroid priming (mean 4.9–5.4 µg/L ±

2.1–3.0) [75]. With sex steroid priming, mean peak GH values after stimulation were 15.4–19.3 µg/L ± 5.1–5.9 using three different priming doses of testosterone. Untreated, the boys' mean HtSDS changed from –2.4 ± 0.4 (range –4.0 to –1.7) at time of testing to –1.27 ± 0.72 (range –2.54 to +0.49) at AH. The resultant HtSDS was within the normal range and commensurate with the boys' MPH. However, there were no data on females, and most of the boys had a normal AH prediction at the time of testing (mean –1.3 ± 1.0 SD, with range from –3.1 SD to +2 SD).

In generating this statement, the guidelines taskforce placed high value on reducing unnecessary GH treatment of children with constitutional delay of growth and puberty, with its associated potential harms (proven or theoretical), costs, and psychological and physical burden. Sex steroid priming was repeatedly shown to increase the specificity, without hampering the sensitivity, of GH provocative testing for severe GHD, but the studies all involved small sample sizes, and there was only one study reporting AH, the chosen outcome to grade the evidence. This study showed that the boys reached normal AHs without GH treatment, but many had predicted AHs in the normal range at the time of testing. While the range of predicted AHs in this study went down to –3.1 SD, group data can obscure changes at the individual level. There is no direct evidence that patients with predicted AH below –2 SD at the time of testing and classified as GH-deficient solely when tested without sex hormone priming achieve a height within the adult normal range without GH treatment. Hence, the evidence was graded as low. The taskforce reached a unanimous consensus that prepubertal children of pubertal age diagnosed with GHD using sex steroid priming likely will experience greater benefit from GH treatment than such children diagnosed without priming. The possibility remains that, of such patients diagnosed as having GHD solely without sex steroid priming, the patients with abnormally low AH predictions at the time of testing may still require GH treatment to achieve a normal AH.

No gynecomastia in boys or other side effects have been reported with the recommended doses of sex steroid priming. No systematic controlled evidence exists to favor any of the proposed protocols over another. Wetterau [76] summarized the various methods used.

2.3. Measurement of spontaneous GH secretion.

2.3.1. We recommend against the use of spontaneous GH secretion in the diagnosis of GHD in a clinical setting. (Strong recommendation, ●●○○)

Given the limitations of provocative testing, the idea of measuring spontaneous secretion as a profile with serial sampling [77] or as an integrated level by continuous withdrawal [78] is attractive. It seems plausible that a child unable to normally secrete GH could still respond to the nonphysiological pharmacology of provocative testing, a condition termed neurosecretory dysfunction [77]. This hypothesis was tested by GH treatment of 7 short children with abnormally low growth velocity, who had provocative responses >10 µg/L but low spontaneous secretion [77]. Short-term acceleration of growth was observed, similar to that seen in children with conventionally defined GHD. Neither long-term growth nor adult-height data were presented. In addition to first-year acceleration of height velocity being a very imperfect predictor of AH gain, a major weakness of this study was that 4 of the 7 patients were of pubertal age with severe bone age delay. Onset of puberty during treatment was not evaluated and could account for much or all of this acceleration. A similar first-year growth acceleration was reported in 2 other studies of children diagnosed by the same criteria [79–81], and both of these studies suffered from the same limitations.

We could find a report of the effects on AH in only one retrospective study [80] that showed a mean AH gain of 1.03 SDS following GH treatment in children who met the criteria for neurosecretory dysfunction, compared to untreated ISS cases with normal spontaneous secretion. This gain is virtually identical to that obtained in treated ISS (see discussion below) making the contribution of the spontaneous GH measurement very questionable.

Normative data for spontaneous GH secretion were established by a study that showed that 4/10 normal-height, normally growing children and 8/35 with constitutional delay, but normal growth velocity, had overnight secretory patterns compatible with the diagnosis of neurosecretory GHD [82]. An additional study also found overlap of spontaneous GH secretion between healthy, normally growing children and children with GHD [83]. Unfortunately, results of frequent GH sampling were inconsistent when normal children were studied on two separate occasions under identical conditions [84]. In light of these limitations, the taskforce felt any potential benefit of overnight GH sampling did not warrant the burden to patients and, hence, rated this recommendation strongly.

3. Dosing of GH Treatment for Patients with GHD

For the indication of GHD, manufacturers of somatropin obtained governmental agency approval for dose

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ranges of 25–35 µg/kg/day or 0.16–0.24 mg/kg/week, as listed in product inserts (so called standard dosing). In the USA, a few manufacturers obtained approval for higher dosing prepubertally (up to 0.3 mg/kg/week or ~42–50 µg/kg/day depending upon dosing of GH 6 days or 7 days per week) and up to 0.7 mg/kg/week during puberty (pubertal dosing; for GHD only). Dosing based upon BSA is also reported in some product inserts used outside the USA. In this section, doses are reported as mg/kg/week or mg/m^2/week. Some studies reported doses in international units (IU). The conversion formula 3.0 IU per 1 mg of GH was used for dose comparison, as most of the studies cited administered authentic rhGH (the conversion formula for methionyl GH, an early GH formulation, is 2.7 IU per 1 mg). Studies reporting doses in mg/m^2 were not converted to mg/kg because weight and BSA change at different rates during childhood, thereby precluding a reliable formula for dose conversion. As a point of reference, for a 30-kg, 1-m^2 child, 0.16–0.24 mg/kg/week equals 4.8–7.2 mg/m^2/week.

3.1. We recommend the use of weight-based or BSA-based GH dosing in children with GHD. (Strong recommendation, ●●●○)

Technical Remark: We cannot make a recommendation regarding IGF-I-based dosing because there are no published AH data using this method. The rationale is logical, but the target IGF-I level has not been established to optimize the balance between AH gain, potential risks, and cost.

Studies demonstrating the positive effects of GH on achieved AH have overwhelmingly used weight- or BSA-based dosing [8–17, 85–88]. Selection of dosing based upon weight or BSA seems to be a matter of personal or national preference [89]. The rationale for using BSA-based dosing draws upon the supposition that drug metabolism does not decrease proportionally to increases in body weight, as it is mainly dependent on extracellular fluid volume, which is weight-independent. Differences in dose calculations between the weight- and BSA-based approaches are most prominent at younger ages and with obesity. Hughes et al. [90] noted that older children receive a lower total GH dose if BSA dosing is used, rather than weight-based dosing. Rigorous studies comparing weight-based with BSA-based dosing have not been conducted; thus, there is insufficient evidence to recommend one dosing regimen over the other.

IGF-I-based dosing of GH treatment has been proposed based on two premises. First, there is large interindividual variation in growth response to the same per kg body weight GH dose, so anthropometric-based dosing may not be optimal for a particular patient. Second, because the growth effects of GH are due in large part to its induction of IGF-I, serum IGF-I concentration can serve as a biomarker of GH action in an individual patient and allow more individualized dose titration, akin to dosing levothyroxine based on thyroid function tests. Cohen et al. [91] evaluated the efficacy of serum IGF-I-based dosing on growth after 2 years of GH therapy in a randomized trial. Children diagnosed with GHD who received GH doses that achieved a serum IGF-I SDS of +2 experienced a statistically significant greater difference in HtSDS (+2.04 ± 0.17 from pretreatment HtSDS) than children randomized to receive GH to achieve a serum IGF-I SDS of 0 (+1.41 ± 0.13 from pretreatment HtSDS). The average GH dose to achieve an IGF-I SDS of +2 was 91 µg/kg/day (median 65 µg/kg/day), while the average GH dose to achieve a serum IGF-I SDS of 0 was 37 µg/kg/day (median 33 µg/kg/day). Within each treatment group, a wide range of doses was needed to achieve the target IGF-I level. With an IGF-I target of +2 SDS, fewer than 65% of children required GH doses above 50 µg/kg/day, while 35% required GH doses of 50 µg/kg/day (~0.35 mg/kg/week) or less. In the IGF-I target of 0 SDS group, fewer than 20% of children required GH doses above 50 µg/kg/day. Thus, some children with GHD experience a more robust rise in IGF-I level (correlated with linear growth) than others on similar weight-based doses [92]. Studies comparing the effectiveness of IGF-I-based dosing with that of standard weight-based dosing on AH have not yet been done. As the panel elected to base recommendations on AH outcomes, there is insufficient evidence at this time to recommend IGF-I-based dosing over weight- or BSA-based dosing.

Thrice weekly (TIW) dosing of GH was used initially after introduction of recombinant GH as a holdover from dosing paradigms used with pituitary-derived GH. Daily dosing of GH resulted in higher absolute height gain and gain in HtSDS than dividing the same weekly dose as TIW in 1–4 years of comparison study [93, 94]. In the studies reporting AH in GH-treated children, dosing of GH was 6–7 days per week in the majority of studies, or a mixture of TIW or more frequent dosing in the remaining. As the bulk of AH data were obtained in persons who received dosing more often than TIW, TIW dosing is not suggested.

3.2. We recommend an initial GH dose of 0.16–0.24 mg/kg/week (22–35 µg/kg/day) with individualization of subsequent dosing. (Strong recommendation, ●●○○)

Technical Remark: Some patients may require higher doses.

The strength of the evidence indicating a difference in AH between children with GHD who receive different doses of GH is moderate-low as studies differ in their conclusions. Given the burden of GH treatment on the health-care system and the unresolved long-term risks of treatment, the lowest dose with demonstrated efficacy should be used.

The body of evidence concerning the effect of different GH dosing regimens on AH outcomes is of moderate-to-low quality. This evidence consists of reports of mean GH doses used in registry- or population-based studies, analyses of potential variables that may affect AH in patients enrolled in registries, and nonrandomized or randomized trials with low patient numbers. Early data from the NCGS and KIGS registries, which included data with higher weekly doses of recombinant GH (0.18–0.3 mg/kg/week) than were used in pituitary-derived GH studies [95, 96], indicated that mean AH SDS-MPH SDS was –0.5 SD with ~0.18 mg/kg/week [10] or –0.5 SD with 0.3 mg/kg/week [11], suggesting that the higher weekly dose of recombinant GH could result in larger height gains over the lower weekly dose that had been used with pituitary-derived GH. Later data with a greater number of enrolled subjects in the French national registry (n = 1,524), Pharmacia/Pfizer registry (n = 1,258), and a Dutch cohort (n = 552), did not find a significant correlation between GH dose and AH on multivariate analysis [9, 12, 97]. Participants in these studies were treated for 4–9 years, and the reported mean GH doses were 0.18–0.24 mg/kg/week with a range between 0.11 and 0.28 mg/kg/week. In a Canadian cohort of 96 patients, a fixed dose of 0.18 mg/kg/week given for an average of 9 years resulted in heights that were within –0.5 SD from MPH [15]. A retrospective case-control study of 26 patients who received 0.15 or 0.3 mg/kg/week found that the 13 patients who received the 0.3 mg/kg/week GH dose achieved a mean AH SDS – MPH SDS 0.73 SD higher than patients who received the lower dose [14]. The participants had similar MPH, baseline height, and treatment duration. An RCT of 35 subjects compared AH in children receiving 0.7 mg/m^2/day (4.9 mg/m^2/week) versus 1.4 mg/m^2/day (9.8 mg/m^2/week) [98]. The mean AH SDS – MPH SDS was –0.7 versus –0.3 SD in the low and high dose groups, respectively, a difference of 4 cm that did not reach statistical significance. This study may have been insufficiently powered to detect a difference, so larger controlled trials may yet demonstrate a statistically significant effect of higher GH doses. In summary, in studies reporting AH, the majority of patients were administered GH doses between 0.18 and 0.24 mg/kg/week

and multivariate analysis of the data did not consistently reveal a correlation between higher dosing and greater AH. Studies directly comparing different dose regimens enrolled small numbers of patients and results differed between studies.

As one of its guiding principles, the guidelines taskforce endorses harm prevention (theoretical or proven) over practices that have unproven benefits. High dosing of GH carries a higher risk of long-term adverse effects theoretically and a certain higher cost burden on healthcare systems. Since the body of evidence is conflicting on the comparative effectiveness of different GH doses on AH, the panel elected to recommend initiation of GH at the lower dose range.

Interindividual variability in growth velocity after initiation of GH, likely reflecting heterogeneity of populations diagnosed with GHD, suggests that subsequent dosing should be individualized. Variables such as first-year growth velocity, height at start, duration of treatment, peak GH concentration during provocative testing, and MPH have been correlated with a taller AH [9, 12]. In efforts to predict individual response to GH from pretreatment characteristics and short-term treatment outcomes, models have been developed using data from registries [7, 56, 99, 100]. Models have been verified retrospectively in two different cohorts of less than 100 children [56]. One study compared growth of children with GHD randomized to receive standard weight-based GH dosing or individualized GH dosing modeled from pretreatment characteristics [101]. After 2 years of treatment, the HtSDS – MPH SDS was similar between the groups (–0.42 ± 0.46 vs. –0.48 ± 0.67), but the individualized GH dose group had a narrower distribution of SDS (range of 2.25 in the individualized group vs. 3.36 in the standard dose group). In other studies, short-term growth endpoints, such as 1- and 2-year growth velocity and change in HtSDS, have been shown to be increased by factors such as higher GH dosing or dose titration to IGF-I levels [92, 102]. Although logical and promising, these strategies to optimize growth parameters in the short term have not been tested to AH. Additionally, the comparative effectiveness of these various strategies has not been tested. Thus, a statement on the most effective strategy to individualize GH dosing after GH initiation (using anthropometric parameters, modeled GH responsiveness, and/or IGF-I levels) cannot be surmised from the available data.

3.3. We suggest measurement of serum IGF-I levels as a tool to monitor. adherence and IGF-I production in response to GH dose changes. We suggest that the GH dose be lowered if serum IGF-I levels rise above the laboratory-

defined normal range for the age or pubertal stage of the patient. (Conditional recommendation, ●○○○)

GH stimulates the synthesis and secretion of IGF-I, whose circulating concentration generally increases with increased GH dose. Thus, serum IGF-I concentration is a useful biomarker of GH exposure both in diagnosis and in treatment monitoring [102]. The target IGF-I level that results in optimal growth while minimizing future theoretical risk is not known. Meta-analysis of cohort and case-control studies in the general non-GH-treated population indicates that serum IGF-I levels in both the low and high ends of the normal range are associated with greater cancer and all-cause mortality [103]. The studies used for the meta-analysis measured IGF-I levels in subjects of various ages from 20 to 98 years, with the majority between ages 40–90 years and the duration of follow-up ranging between 5 and 18 years. The long-term effects of briefer periods of higher IGF-I levels in childhood are not known.

The long-term risks of higher IGF-I levels of short or long duration are not resolved. The consensus panel endorses harm prevention in the treatment of children with GH. As long as the potential risk is unresolved, we suggest that the serum IGF-I concentration be monitored on a regular basis with the goal to keep IGF-I levels in the normal range for age and pubertal status. Assays used to quantify IGF-I include immunometric and liquid chromatography/tandem mass spectroscopy techniques. Available commercial assays may provide different IGF-I values when applied to the same serum sample [104]. For that reason, when making clinical decisions for an individual, the IGF-I values must be interpreted against the gender-, age-, and puberty-specific reference ranges provided by the commercial laboratory used in measuring that value. Levels of IGF-binding protein 3 (IGFBP-3) and acid-labile subunit have also been associated inconsistently with risk of certain cancers, and modulate the bioavailability of IGF-I. However, the complex interactions among the three proteins have not been studied sufficiently to support using alternative markers (e.g., molar ratio of IGF-I/IGFBP-3 as an estimation of free IGF-I) to predict long-term risks [105–107].

3.4. During puberty, we recommend against the routine increase in GH dose to 0.7 mg/kg/week in every child with GHD. (Strong recommendation, ●●○○)

The FDA approved higher GH dosing during puberty based on results of an RCT [85] in which individuals who received the higher GH dose of 0.7 mg/kg/week during 3 years of puberty had a higher growth velocity and achieved a higher AH SDS. The absolute difference in mean AH between the high dose and control dose (0.3 mg/kg/week) groups was 4.6 cm after 3 years and 5.7 cm after 4 years. Although MPH SDS between the two groups was not different at baseline, AH SDS – MPH SDS was not reported; the effect of therapy experienced by the individual may well be different from the group. The control dose group achieved median IGF-I levels of 615 µg/L (range 139–1,079) whereas the high dose group achieved IGF-I levels of 910 µg/L (range 251–1,843) after 36 months of therapy. Of the 97 subjects enrolled, 10 experienced serious adverse events, 4 in the standard dose group and 6 in the high dose group. Four of the 48 patients receiving the higher dose experienced effects consistent with GH excess, such as enlarging shoe size, ankle swelling, and hip pain. Although no cases of intracranial hypertension or slipped capped femoral epiphysis were reported, the study was not adequately powered to detect these potential serious side effects.

Randomized studies comparing pubertal doses lower than 0.7 mg/kg/week to standard dosing have also been performed [108–110]. Ninety-two Swedish children were randomized to standard dosing (0.1 IU/kg/day, ~33 µg/kg/day) or pubertal dosing once or twice daily (0.2 IU/kg/day, ~67 µg/kg/day) at Tanner stage 2 [109]. Median AH SDS – MPH SDS was between 0 and 1 SD for all groups with a similar distribution of data. Another study randomized 49 adolescents to standard dosing (0.7 mg/m^2/day) or pubertal dosing (1.4 mg/m^2/day) at Tanner stage 2 [110]. Mean AH SDS – MPH SDS (0.1) was not different between groups. Using data from the KIGS database, multiple linear regression analysis revealed that gender, age at puberty onset, and height at puberty onset were associated more strongly with pubertal growth than was GH dose [111].

Members of the consensus panel unanimously agreed that the high rate of observed effects consistent with GH excess and the untested potential for more adverse effects in a greater sample size carried an undesirable risk of harm to patients receiving the 0.7 mg/kg/week dose. This concern, coupled with the unresolved long-term risk of higher dose of GH and health-care cost burden of the 0.7 mg/kg/week dose, prompted the consensus panel to recommend against the routine use of this dose during puberty.

3.5. We recommend that GH treatment at pediatric doses not continue beyond attainment of a growth velocity below 2–2.5 cm/year. The decision to discontinue pediatric dosing prior to attainment of this growth velocity should be individualized. (Strong recommendation, ●●○○)

Studies describing the effect of GH on the outcome of AH have involved treatment to AH or near-AH as defined by extremely slow growth rate and/or attainment of a specified skeletal maturation [8–17, 85–88]. Across studies, growth rates used to define near-AH and consideration of GH discontinuation varied from 0.5 to 3 cm/year, with the majority of studies using rates between 2 and 2.5 cm/year. Definition by bone age also varied across studies, with 14–15 years used for girls and 16–17 years used for boys. There have been no studies comparing AH in persons in whom therapy was deemed complete at a certain growth rate versus a certain bone age. Although evidence behind the recommendation is of low quality, the taskforce agreed that acromegalic changes are possible with use of pediatric GH doses in adolescents with fused epiphyseal plates and should be avoided. Because of the potential for benefit regarding certain metabolic parameters, the panel recommends evaluation for persistent GHD, as detailed below.

The guidelines taskforce recognizes that the risk and logistics of GH therapy to achieve a specific height goal may differ between individuals, so it may be appropriate to discontinue GH therapy earlier in some individuals. This decision may be influenced by the clinical factors surrounding the diagnosis of GHD; many children with idiopathic IGHD have normal test results when the GH axis is re-evaluated upon achievement of AH [112]. Additionally, re-examination of the GH axis 1 or more years after diagnosis of idiopathic IGHD in still growing children can yield normal results in a majority of patients [113]. In a nonrandomized study, patients who re-tested normal during puberty and discontinued GH achieved an AH SDS – MPH SDS similar to children who re-tested as having GHD and remained on GH treatment; the absolute height in centimeters was not significantly different between groups [114]. One study reporting on patients who ended treatment prior to attainment of AH found their achieved heights were similar to those who maintained treatment until growth plate fusion [12], though the "stopped early" group was not defined. These data raise the question as to whether all children diagnosed with IGHD need to continue GH treatment until growth plate fusion to achieve target AH.

4. Safety Issues of GH Treatment for Patients with GHD

On-treatment safety and adverse effects of GH therapy [115] have been extensively tracked and reviewed for children with GHD (isolated or as part of MPHD) and ISS [1, 116]. Available information, derived mainly from postmarketing surveillance studies maintained by GH manufacturers (e.g., KIGS and NCGS) [115, 117], indicates a low frequency (i.e., <3% of treated children) of adverse effects and reinforces a favorable on-treatment safety profile of GH. The size and duration of these postmarketing studies provides reassurance that on-treatment adverse events that are either frequent or have catastrophic consequences are not being missed. However, the full spectrum of potential GH adverse effects is not comprehensively or accurately elucidated by postmarketing surveillance studies due to: (1) inherent weaknesses in patient cohort surveillance such as dependence on physician reports of occurrence and uncertain relevance to GH treatment; (2) changes over time in GH dosage and/or recipient characteristics that may alter risk for adverse effects; (3) failure to capture adverse events that only become manifest after treatment; and (4) lack of a valid control population for comparisons. Thus, all potential risks should be evaluated with regard to the underlying diagnosis and individually before initiating GH treatment.

4.1. We recommend that prospective recipients of GH treatment receive anticipatory guidance regarding the potential adverse effects of intracranial hypertension, SCFE, and scoliosis progression. (Ungraded good practice statement)

4.2. We recommend monitoring of GH recipients for potential development of intracranial hypertension, SCFE, and scoliosis progression by soliciting pertinent history and performing a physical examination at every follow-up clinic visit; further testing should be pursued if indicated. (Strong recommendation, ●●●●)

(A) Intracranial hypertension

Intracranial hypertension may occur with GH therapy [118]. It occurs at an overall incidence of 28 per 100,000 treatment-years, with a higher rate among patients with chronic renal insufficiency, Turner syndrome, and organic GHD, and at a lower rate in patients with ISS. It generally occurs during treatment initiation or dosage increases, and reverses with discontinuation of GH. A referral for formal funduscopic examination by an ophthalmologist is advised if symptoms suggestive of intracranial hypertension occur such as severe headache, double/blurry vision, and vomiting. Treatment can often be reinstituted at lower doses without return of symptoms.

(B) Slipped capital femoral epiphysis

SCFE is reported at an incidence of 73 per 100,000 treatment years and occurs less frequently in patients

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with IGHD (18.3) and ISS (14.5) compared to those with GHD due to intracranial neoplasms (86.1), craniopharyngioma (120), or after stem cell transplantation [119, 120]. The median duration from onset of GH therapy to SCFE ranges from 0.4 to 2.5 years. Routine monitoring for suggestive symptoms such as hip and/or knee pain and changes in gait is advised and, if positive, careful physical examination and consideration of imaging and orthopedic specialty consultation. SCFE requires surgical pinning of the capital femoral epiphysis to correct its malposition.

(C) Scoliosis progression

Scoliosis progression during GH therapy appears due to rapid growth rather than as a direct side effect of GH per se. Scoliosis is observed in ~0.2% of children with ISS or IGHD treated with GH [102], less frequently than in diagnostic groups with a higher baseline incidence (e.g., Turner syndrome and Prader-Willi syndrome) [121]. Routine examination for scoliosis presence or progression is advised in recipients of GH treatment.

4.3. We recommend re-assessment of both the adrenal and thyroid axes after initiation of GH therapy in patients whose cause of GHD is associated with possible MPHD. (Strong recommendation, ●●○○)

Technical Remark: Evaluate for possible central adrenal and thyroid insufficiencies in those not yet diagnosed, and consider increasing hydrocortisone and/or levothyroxine doses in those already on these hormone replacement(s).

Physiological effects of GH on glucocorticoid metabolism (i.e., reducing hepatic 11β-HSD1-mediated conversion of inactive cortisone to active cortisol and increasing CYP3A4-mediated cortisol catabolism) raise theoretical concerns that GH treatment could make manifest an underlying adrenal insufficiency. While adrenal insufficiency has been identified as a predominant cause of preventable deaths in long-term follow-up of pituitary GH recipients [122], more recent data indicate a rate of adrenal insufficiency in GH recipients (most of whom did not have MPHD) equal to that expected for the general population [115], suggesting association of adrenal insufficiency and GH treatment rather than causality.

Similarly, GH can lower serum free T4 concentrations, often used to diagnose central hypothyroidism, by increasing the peripheral deiodination of T4 to T3 [123].

4.4. We recommend discussion about and monitoring of glucose metabolism of GH recipients who are at increased risk for diabetes due to insulin resistance. (Ungraded good practice statement)

The incidence of type 1 diabetes mellitus (DM) is not increased by GH therapy. However, carbohydrate metabolism is altered during GH therapy of children with either IGHD (i.e., restoration of normal insulin sensitivity) or ISS (i.e., decrease in insulin sensitivity and compensatory increase in insulin secretion with maintenance of euglycemia) [124–127]. Thus, children with type 1 DM will require higher doses of insulin if/when concurrently treated with GH. In children with compromised insulin secretion or sensitivity, GH may induce glucose intolerance and manifest hyperglycemia in the prediabetic phase of type 1 DM. Reported effects on the incidence of type 2 DM include both an increase [128] and no change in incidence [115] compared to population expectations. To date, overall data suggest: (1) decreases in insulin sensitivity are concurrent with GH therapy and return toward normal with cessation of treatment; (2) no clear adverse effects on glucose metabolism during and following GH therapy; and (3) monitoring for potential development of diabetes with blood testing for glucose and/or HbA1c levels should be focused on GH recipients at high risk [129].

4.5. Counseling prospective recipients of GH treatment regarding the risk of neoplasia

4.5.1. We recommend informing at-risk patients about available data and encourage long-term follow-up with their oncologist. (Ungraded good practice statement)

4.5.1.1. For children with acquired GHD due to effects of a primary malignancy:

4.5.1.1.1. We recommend shared decision-making that involves the patient, family, oncologist, and treating endocrinologist. Before initiation of GH treatment, we recommend sharing with families the most recent data about risks, including the potential effect of GH treatment on the timing of second neoplasm occurrence. (Ungraded good practice statement)

4.5.1.1.2. For GH initiation after completion of tumor therapy with no evidence of ongoing tumor, a standard waiting period of 12 months to establish "successful therapy" of the primary lesion is reasonable, but can also be altered depending on individual patient circumstances. (Ungraded good practice statement)

Technical Remark: Although many of the intracranial tumors are not "malignant" (i.e., craniopharyngioma), they have the potential to recur. There are no data to suggest treating them differently than malignant tumors with regard to observation periods before initiating GH treatment.

4.5.1.2. In the rare situation where a child with GHD has an accompanying condition with intrinsic increased risk for malignancy (e.g., neurofibromatosis-1, Down

syndrome, Bloom syndrome, Fanconi anemia, Noonan syndrome, and Diamond-Blackfan anemia), we recommend providing counseling regarding the lack of evidence concerning GH effect on malignancy risk in these groups. (Ungraded good practice statement)

4.5.2. For children considered not to be at risk, we recommend that counseling includes information about the unknown long-term (i.e., posttreatment) risks of neoplasia still being studied. (Ungraded good practice statement)

Pathophysiological and epidemiological observations prompt concern that GH might increase risk of malignancy during or after therapy. IGF-I and GH are mitogenic, anti-apoptotic, and their receptors are found in tumors. States of impaired [130] and excess [131] GH secretion/action are associated with reduced and increased malignancy risk, respectively. Reduction in IGF-I via caloric restriction induces apoptosis and prevents or slows tumor growth [132]. Some, but not all, epidemiological studies associated increases in GH and IGF-I levels with colon, breast, thyroid, and prostate cancer [133]. A retrospective analysis of adults who received human pituitary-derived GH as children suggested an increased mortality rate from colon cancer and Hodgkin disease, but based on only two cases of each type of malignancy [134]. Overall, the data suggest a permissive/facilitative rather than causative role for GH in oncogenesis [135].

Current evidence indicates the following general conclusions regarding GH treatment in children with GHD, small for gestational age (SGA), or ISS: (1) incidence of new-onset leukemia during treatment [115] or malignancies in general following treatment [136–139] in children without associated risk factors is not increased compared with that in the age-matched general population; (2) any increased risk for new-onset leukemia appears limited to children with underlying conditions that already predispose them to develop malignancies [140]; (3) tumor recurrence is not increased in persons successfully treated for their primary lesion [141, 142]; and (4) GH treatment of children with a history of malignancy (particularly when treated with radiation) may slightly hasten the appearance of a second neoplasm [142, 143] but does not appear to increase the overall risk of second neoplasm occurrence [144] when compared to patients not treated with GH [143]. While analysis of available data is complicated by the elevated risk for malignancy in any child with a prior malignancy, and single institution studies have reported absence of GH effect on second neoplasm occurrence [145–147], an increased risk of developing second neoplasms in GH-treated childhood cancer survivors is currently listed in US labeling for all GH products. Data are lacking regarding GH effects on the risk of neoplasia in patients with conditions already associated with an intrinsically increased malignancy risk [148-153]. Risk of neoplasia in pediatric patients treated with GH was reviewed extensively by the PES Drug and Therapeutics Committee, with a key recommendation being that ongoing long-term posttreatment surveillance of GH recipients is paramount [154].

4.6. We recommend that prospective recipients of GH treatment be informed about the uncertainty regarding long-term safety (posttreatment adverse effects in adulthood). (Ungraded good practice statement)

Long-term follow-up (mean 17 years) of 6,928 children with IGHD, ISS, or a history of being born SGA who started GH treatment between 1985 and 1996 in France revealed a 30% increase in all-cause mortality compared to the general population [136]. All type cancer-related mortality was not increased, but standardized mortality rates (SMR) were increased for bone tumor-related (5.00; CI 1.01–14), circulatory system (3.07; CI 1.4–5.8), and cerebral hemorrhage (6.66; CI 1.8–17) events. Dosage of GH >50 µg/kg/day conferred an SMR of 2.94. Derived from the same database, a recent study reported a significantly higher risk of stroke (particularly hemorrhagic stroke) among patients treated with GH in childhood [155]. In contrast, follow-up of 2,543 IGHD, ISS, and SGA patients from other European countries, for whom vital status data were available for 98%, revealed no effect of GH exposure and/or dosage on mortality or the incidence of cardiovascular events [137]. A separate study devised an advanced model that adjusted for birth weight, birth length, and neonatal health to estimate SMR using the Swedish Medical Birth Registry. Applying the advanced model to GH-treated Swedes (n = 3,847) with IGHD, ISS, or SGA, the SMR with GH treatment was 0.955 (CI 0.591–1.456) [139]. Validity of reports from the French data could be confounded by lack of an untreated control population, appropriateness of the reference population chosen, a large number of "idiopathic deaths," and missing data about GH treatment details and concomitant conditions.

In summary, available data support the following conclusions regarding safety of GH therapy for children with IGHD, organic GHD, and ISS: (1) certain adverse effects associated with rapid growth (scoliosis progression and SCFE) and others of unknown mechanism (intracranial hypertension) occur rarely and merit anticipatory guidance and close monitoring; (2) insulin sensitivity is reduced, but overt hyperglycemia is rare (increased risk for

type 2 DM is not evident overall, but should be considered in patients already at higher risk); (3) levels of endogenous cortisol can decrease due to effects of GH on glucocorticoid metabolism, so that GH therapy in severe GHD may unmask previously unsuspected central adrenal insufficiency; and (4) GH does not increase risk for new malignancy in children without risk factors, and current data suggest that GH treatment has a slight-to-absent effect on increasing or hastening onset of second neoplasms in patients previously treated for cancer, particularly when such treatment includes cranial irradiation.

With regard to potential adverse effects of GH in general, caution is warranted when extrapolating findings from earlier studies to future safety of GH [156]. Increasing dosages of GH, like spontaneous GH excess, could increase the chances for remote metabolic or malignancy risks not detected in current analyses. Most patient-years available for analysis involve administration of GH doses used for hormone replacement for GHD (<0.3 mg/kg/week), whereas the expanding cohort of non-GHD patients includes those receiving pharmacological doses of GH (e.g., 0.375 mg/kg/week for ISS [140] and 0.7 mg/kg/week for "pubertal dosing" [85]). Change in recipient characteristics due to ethnic demographics and rising childhood obesity rates could increase risk for type 2 DM precipitated by GH. Moreover, drug adverse events can occur remotely after the drug has been discontinued, but only adverse events occurring during GH therapy have been tracked in postmarketing surveillance studies; detection of subsequent adverse effects depends on physician-initiated reports to monitoring agencies. Since studies of non-GH-treated populations suggest that high-normal levels of free IGF-I (often seen in GH-treated children) may increase rates of breast and prostate cancers, a potential relationship between GH exposure and future risk for neoplasia requires continued vigilance. Finally, the appropriate level of risk to be tolerated for the newest and potentially largest GH-treated group in the future – essentially healthy, but short children – remains to be defined [157].

5. Transitional Care after Childhood GH Treatment

Adults with childhood-onset GHD can have alterations in body composition, bone mineral density, and lipid metabolism that are mitigated by GH treatment [20]. Yet a number of children with a diagnosis of GHD have a normal somatotropic axis upon retesting in late adolescence [112, 158–160]. Therefore, re-evaluation of the somatotropic axis in children diagnosed with GHD is required during the so-called transition period. The transition period is the time from late puberty to establishment of adult muscle and bone composition, and encompasses attainment of AH. As attainment of adult or near-AH is an easily measurable variable, re-evaluation of the somatotropic axis is most conveniently performed when growth has slowed to the point when pediatric GH dosing will be discontinued, as detailed above.

5.1. We recommend that patients with multiple (≥3) pituitary hormone deficiencies regardless of etiology, or GHD with a documented causal genetic mutation or specific pituitary/ hypothalamic structural defect except ectopic posterior pituitary, be diagnosed with persistent GHD. (Strong recommendation, ●●●○)

Individuals with MPHD, defined as three or more pituitary hormone deficiencies, develop metabolic alterations associated with adult GHD [161, 162] and meet adult criteria for GHD upon GH provocative testing in the transition period [160, 163–165]. Individuals with MPHD also have persistent GHD if provocative testing is repeated later in adulthood [166–168]. GHD is persistent in these individuals whether the MPHD is due to known underlying causes (organic) or idiopathic. In persons with two pituitary hormone deficiencies on a nonorganic basis, they may or may not test as possessing persistent GHD on provocative testing; thus, provocative testing is advised (see below). Adolescents with IGHD and structural pituitary defects such as absence of the pituitary stalk meet criteria for adult GHD [164, 169, 170] when tested. Persons with small pituitary glands at diagnosis have a high rate of testing normal when retested after completion of growth [164, 171]; thus, a small pituitary is not considered a structural defect. The risk of persistent GHD in individuals with ectopic posterior pituitary varies according to their pituitary structure, as discussed in section 5.2.

Adolescents with MPHD or a structural defect (except ectopic posterior pituitary, see discussion below) have a nearly 100% fail rate on GH provocative testing [160, 163–165, 172]. Hence, an IGF-I measurement off GH therapy in these persons is not necessary. Although an IGF-I level may be obtained off GH treatment to confirm the diagnosis of persistent GHD to the patient, the patient's family, or a third-party payer, a significant number of persons with MPHD can have an IGF-I concentration in the normal range [167]. Thus, the results of IGF-I testing must be interpreted carefully.

5.2. We recommend re-evaluation of the somatotropic axis for persistent GHD in persons with GHD and deficiency of only one additional pituitary hormone, idiopathic IGHD, IGHD with or without a small pituitary/

ectopic posterior pituitary, and in patients after irradiation. (Strong recommendation, ●●●○)

Technical Remark: Testing can be performed after a trial of at least 1 month off GH treatment.

Individuals with GHD and deficiency of only one additional pituitary hormone may or may not have persistent GHD upon testing [164, 167, 173, 174]. Individuals with an ectopic posterior pituitary gland associated with pituitary stalk agenesis have persistent GHD [164] while those with a normal pituitary stalk tend to have normal GH levels upon provocative testing in the transition period [171]. However, in a small study, when individuals with an ectopic posterior pituitary gland and normal GH provocative testing on initial re-evaluation were retested 2 years later, GH provocative testing indicated GH peak <5 μg/L and worsening lipid function compared to controls [175]. This suggests a need for more studies to determine the frequency and best practices for the re-assessment of these patients over time. In the absence of data, it is prudent to follow persons with ectopic posterior pituitary who tested GH sufficient, and consider testing of the somatotropic axis more than once in the transition period.

The development of GHD after radiation treatment is dose and time dependent [176, 177]. A large percentage of adolescents with radiation-induced GHD diagnosed and treated in childhood do not meet criteria for adult GHD on retesting [178]. Those who re-tested as having persistent GHD had received the highest radiation dose or passed the longest duration since radiation treatment. Considering the evolution of radiation-induced GHD, individuals who initially re-test GH-sufficient should be monitored over time, similar to persons with ectopic posterior pituitary.

5.2.1. We suggest that measurement of the serum IGF-I concentration be the initial test of the somatotropic axis if re-evaluation of the somatotropic axis is clinically indicated. (Conditional recommendation, ●○○○)

Individuals with idiopathic IGHD and serum IGF-I greater than 0 SD for age are highly likely to have normal GH provocative testing. Thus, provocative testing appears unnecessary in these individuals. The remaining individuals should undergo GH provocative testing.

Individuals diagnosed with idiopathic IGHD have a high likelihood of retesting sufficient on GH provocative testing [112, 159, 160, 166]. In many series, individuals with idiopathic IGHD and an IGF-I concentration >0 SD do not meet criteria for adult GHD on re-testing [159, 160, 172, 179, 180]. Many adolescents with an IGF-I level greater than 0 SD will have normal results on provocative

testing, but the absolute IGF-I cutoff value below which children re-test as having persistent GHD varies between studies and, thus, is not clear [159, 160, 169, 172, 179, 180]. Individuals with idiopathic IGHD who re-test sufficient on provocative testing have normal metabolic functioning upon follow-up [181, 182].

Individuals with MPHD who subsequently test as having persistent GHD on provocative testing can have IGF-I levels in the normal range [159, 160, 169, 172, 179, 180]; thus, a normal IGF-I level does not preclude the need for provocative GH testing. The metabolic status later in life of individuals with discordant IGF-I and GH provocative testing results is not clear. In these cases, the clinical scenario is often used to consider the diagnosis of persistent GHD. Observation and repeat testing may be necessary in these individuals.

IGFBP-3 is often used to assist in the diagnosis of GHD in children. One study of 55 US children found that an IGBP-3 level less than −2 SD conferred a specificity of 100% and sensitivity of 35% in the diagnosis of persistent GHD in the transition period [160]. However, no other study investigated the diagnostic performance of IGFBP-3 testing in the transition period, and IGFBP-3 testing is not routinely used in the diagnosis of GHD in adults. For these reasons, recommendations for IGFBP-3 testing in the transition period are not provided.

5.2.2. We recommend GH provocative testing to evaluate the function of the somatotropic axis in the transition period if indicated by a low IGF-I level. (Strong recommendation, ●●●○)

The insulin tolerance test (ITT) has been validated for the diagnosis of adult GHD [20, 168] and persistent GHD in the transition period [165, 172, 179]. During an ITT, a GH cutoff of 5.6 μg/L using an immunometric assay had the highest diagnostic accuracy for predicting persistent GHD [179] with a sensitivity of 77%, specificity of 93%, and correct classification of 87% of patients. This is similar to the cutoff of 5.1 μg/L found to be most accurate in adults (96% sensitivity and 92% specificity) [168]. The diagnostic threshold with the optimal sensitivity and specificity upon GH-releasing hormone (GHRH)-arginine testing in the transition period varied between studies [165, 180] and was higher than in adults [168]. GHRH-arginine test results may be falsely normal in individuals with hypothalamic dysfunction.

Although the ITT has been validated for diagnosis of persistent GHD in the transition period, it is contraindicated in some individuals and is not practical in many endocrine practices due to the risks of symptomatic hypoglycemia. Additionally, GHRH is currently unavailable

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in the USA, so alternative testing methods are desired. Arginine-L-dopa testing has not been systematically tested in the transition population and in adults poorly predicts GHD [168]. Glucagon stimulation testing is a promising alternative for provocative testing in adults [183, 184], but has not been specifically tested in the transition period.

5.3. We suggest that GH treatment be offered to individuals with persistent GHD in the transition period. There is evidence of benefit; however, the specifics of the patient population that benefits, the optimal time to re-initiate treatment, and the optimal dose are not clear. (Conditional recommendation, ●●○○)

Technical Remark: The transition period is the time from late puberty to establishment of adult muscle and bone composition, and encompasses attainment of AH.

Young adults with childhood-onset GHD have lower bone mineral density, lower lean mass, and may have a more unfavorable cholesterol profile with lower HDL and higher LDL than individuals with adult-onset GHD [161, 162, 174, 185–187]. Three RCTs in young adults with persistent GHD indicated that 2 years of GH treatment increased bone mineral density, normalized IGF-I levels, and improved lipid profiles from baseline [188–191]. Participants who did not receive GH treatment had a decline in bone mineral density, persistently abnormal serum IGF-I concentrations, and more unfavorable lipid profiles than at baseline. The majority of patients in these studies had MPHD, the duration off GH was 1–6 years, and the average age at re-initiation of GH treatment was 18–23 years with a range of 15–35 years. A fourth RCT did not demonstrate, after 2 years of GH treatment, a difference in bone mineral density or lipids from baseline, compared to nontreated GHD patients or compared to normal controls [181]. A large proportion of participants in this study had IGHD and the average age at transition was 16 years. Additionally, the duration off pediatric doses of GH was 1 month per study design. The variability in the effect of GHD and GH treatment among these studies suggests that GH efficacy in the persistent GHD population is dependent on age, duration off GH, and etiology. These factors must be taken into account in discussing with adolescents the benefits of GH replacement in the transition period.

The optimal GH dose during the transition period is not clear. The RCTs used GH doses that varied from 12.5 to 25 µg/kg/day (weight-based) to 200 µg/day (fixed dosing). The physiological decline in GH secretion and IGF-I levels with age in adults is well described [192, 193]. Thus, young adults may need higher GH doses than older adults for the same metabolic effects. The optimal dose to achieve the desired metabolic effects in young adults is not established. The Endocrine Society Guidelines for Evaluation and Treatment of Adult Growth Hormone Deficiency suggest that patients <30 years of age may benefit from initial doses of 400–500 µg daily (as opposed to the initial doses of 200–300 µg daily for patients aged 30–60 years), and those transitioning from pediatric to adult replacement may need even higher doses. Females receiving oral estrogen (but not transdermal) may need higher doses than other patients. Doses subsequently should be titrated to normalize the serum IGF-I concentration for age and gender [20]. This is a reasonable approach considering the variability of dosing patterns used in the RCTs.

6. GH Treatment of Patients with ISS

6.1. In the USA, for children who meet FDA criteria, we suggest a shared decision-making approach to pursuing GH treatment for a child with ISS. The decision can be made on a case-by-case basis after assessment of physical and psychological burdens, and discussion of risks and benefits. We recommend against the routine use of GH in every child with HtSDS less than –2.25. (Conditional recommendation, ●●●○)

Technical Remark: While studies have shown GH treatment increases the mean height of treated cohorts, there is marked interindividual variability in responses including some individuals who do not respond to treatment.

6.2. We suggest a follow-up assessment of benefit in HtSDS and psychosocial impact 12 months after GH initiation and dose optimization. (Conditional recommendation, ●●○○)

GH increases AH in some children with ISS, defined by the FDA as stated above in the introduction. As outlined by the ICPED, ISS is heterogeneous and includes familial ISS and nonfamilial ISS, both with and without pubertal delay [4]. Genetic disorders, including genetic mutations affecting the growth plate such as SHOX and NPR2 defects, must be excluded; it is important to assess body proportions in all children with short stature to diagnose conditions that result in disproportionate short stature [194, 195]. The prediction of an individual's spontaneous AH involves the utilization of information about parents' heights, bone age, and growth in untreated cohorts to determine the assumed height target. Patients with ISS and their families should be counseled about heterogeneity in response to GH; i.e., while on average there will be an approximately 5-cm (2-inch) increase in AH

with approximately 5 years of GH treatment, individual responses are highly variable, including no measurable increase in HtSDS in some patients.

There are 3 RCTs with GH treatment to AH [196–198]; only 1 had a placebo control arm [197]. These studies differed on criteria for diagnosis of GHD versus ISS (i.e., cutoff value on GH provocative testing), whether children with a history of SGA were included, GH dose used (0.22–0.47 mg/kg/week), frequency of injections (3–7 per week), and mean duration of treatment (4.6–6.2 years). Combining the 3 RCTs and not excluding SGA, 237 subjects were studied (152 treated and 85 controls), 146 of whom were treated per protocol until near AH or AH (100 treated and 46 controls). One trial ($n = 18$) studied only females [196]. A systematic review by Deodati and Cianfarani [199] reported that the mean height gain of GH-treated children in these 3 RCTs exceeded that of control children by 0.79 SDS (95% CI 0.50–1.09, $p <$ 0.001), or 4.7 cm (1.85 inch). In the largest RCT [196–198], the mean HtSDS attained for non-SGA ISS subjects treated per protocol ($n = 68$) with GH 67 µg/kg/day (0.47 mg/kg/week) or 33 µg/kg/day (0.23 mg/kg/week) was –1.5 and –1.7, respectively, versus –2.2 for controls, with mean gain in HtSDS of 1.3 and 1.2, respectively, versus 0.4. Thus, mean improvement over controls was about 5 cm (~2 inches). Many patients in all 3 groups achieved AH still below –2 SD, and there was only 1 patient with an AH above average (in the higher dose group). However, there was significant variability in responses between individuals, with subsets of patients responding to GH therapy much better or worse than others. Specifically, taller parents, greater delay in bone age, and taller predicted height at enrollment were associated with a greater increase in HtSDS (see below). None of the studies correlated growth velocity to AH, which would allow some prediction of achievable AH using growth velocity response.

There are several other studies to AH that used historical or no controls, many of which relied on the outcome of AH relative to predicted AH, which may overestimate improvement. A meta-analysis by Finkelstein et al. [200] of 10 controlled trials and 28 uncontrolled trials, only 4 to AH, suggested an average gain in AH from GH therapy of approximately 4–6 cm (range 2.3–8.7 cm), with an average of about 1 cm per year of treatment. A study by Sotos and Tokar [201] reported a gain in HtSDS of +1.9 (±0.76) in GH-treated (0.32 ± 0.03 mg/kg/week) children with ISS versus +0.49 SDS (0.18–0.8 SDS) in untreated children with ISS for a net gain of 1.41 SDS. The limitation of this study is that it was a retrospective study,

not an RCT. Additionally, the data for the untreated control group were historical data from 9 different published studies.

Patients and their parents/guardians should be counseled that not starting GH therapy at all is an option. Since not all children with ISS will respond to GH therapy, HtSDS improvement after 12 months of therapy should be assessed, and the discontinuation of GH therapy should be considered if adequate height gain has not been achieved. Models utilizing the first year change in growth rate may assist in predicting longer term response [202, 203]. Additionally, patients should be monitored for changes in psychological functioning and quality of life; better clinical tools for these outcomes need to be developed and validated for this patient population.

6.3. Because there is overlap in response between dosing groups, we suggest initiating GH at a dose of 0.24 mg/kg/week, with some patients requiring up to 0.47 mg/kg/week. (Conditional recommendation, ●●○○)

The approved GH doses are based on the doses used in the studies and may not be optimal for the diagnosis of ISS in general or for individual patients. There is considerable interpatient variability in growth responses without a clear dose-response relationship between change in HtSDS and dose of GH administered to patients with ISS, so the lowest dose of GH with demonstrated efficacy should be used. Because partial or lesser degrees of GHD and ISS may have similar presentations and laboratory findings, it is reasonable to initiate treatment using the upper range of GHD dosing and then titrate upward as necessary. There are no data to support weight-based dosing >0.47 mg/kg/week and, given the unresolved long-term risks of treatment, there should be caution in using higher doses. GH therapy should be discontinued in patients who do not respond.

Only one study of dose effect, that of Albertsson-Wikland et al. [198], included an untreated control group (see section 3.1.1). In the study's ISS per protocol subjects, the difference in gain in HtSDS between 0.23 and 0.47 mg/kg/week (33 and 67 µg/kg/day) was nonsignificant, and was borderline significant ($p = 0.056$) in the combined ISS and SGA group. Wit et al. [204] compared growth responses in 239 children, only 50 to AH. There were no untreated controls, and the subjects received 0.24 mg/kg/week, 0.24 for the first year then 0.37 mg/kg/week thereafter, or 0.37 mg/kg/week with a mean change in HtSDS from baseline of 1.55 ± 0.14, 1.52 ± 0.27, and 1.85 ± 0.2, respectively (statistical testing not performed between groups), suggesting that increasing the dose by 50% may not add sig-

nificant benefit in the majority of patients. A study of 15 subjects with ISS and no untreated controls found no difference in AH using 0.5 or 1 U/kg/week, roughly equivalent to 0.17 or 0.33 mg/kg/week [205]. No data exist to support advantages of weight-based dosing at >0.47 mg/kg/week in children with ISS. Short-term data suggest that targeting GH dosing to IGF-I levels may improve the growth response [91, 92, 206, 206], but there are no data to AH.

Predictors of response to GH have not been validated in controlled studies. There is likely a continuum of responsiveness to GH. Based on modeling from the KIGS database by Ranke et al. [111, 202], determinants may include height deficit relative to genetics (HtSDS – MPH SDS) and earlier age at treatment start (<10 years in boys and <9 years in girls). Total gain in height seems to correlate with first-year responsiveness, while bone age delay may [198] or may not be predictive [111, 202]. Albertsson-Wikland et al. [207] also found on re-analysis that height difference with respect to parents, as well as HtSDS and IGF-I SDS at baseline, explained some of the variance of the responses in their study. In a further analysis of these data, Kristrom et al. [208] determined that the change in IGF-I SDS from baseline to mean study level was the most important determinant in the long-term growth response; the lower the IGF-I SDS at baseline, the higher was the on-treatment increment in IGF-I SDS. While higher GH doses were associated with greater change in IGF-I SDS, there was considerable overlap in responses between dosing groups, suggesting that not all patients require higher doses of GH to achieve a good response.

Defining an adequate growth response is challenging. The actual increase in annualized growth velocity that results in a gain in height relative to age and gender is dependent on age; younger prepubertal and pubertal children grow faster than older prepubertal children. Likewise, the equivalent height in centimeters corresponding to 1.0 HtSDS increases over time. To date, there is no consensus as to what comprises an adequate short-term first-year growth response [209]. At ages 3–8 years, healthy children may have a normal increase in HtSDS of <0.3 [210]. Many studies use an increase in HtSDS of greater than 0.3–0.5 over 1 year. These values were also suggested in a consensus statement from the Growth Hormone Research Society, PES, and the European Society for Pediatric Endocrinology (ESPE) [211]. Additionally, there are published height velocity targets for the first year of GH therapy to use as reference [203].

7. IGF-I Treatment of Patients with PIGFD

7.1. We recommend the use of IGF-I therapy to increase height in patients with severe PIGFD. (Strong recommendation, ●●●●)

Laron syndrome/GHIS, caused by mutations in the GHR gene, is the most common and prototypical condition within the PIGFD category. Untreated patients with Laron syndrome have heights –4 to –10 SD during childhood that persist into adulthood, with AHs of 106–142 cm in males and 95–136 cm in females [212–215]. Treatment with IGF-I for a mean duration of 10 years to adult or near-AH (defined as bone age at least 16 years for males and 14 for females) was reported in 21 patients with PIGFD (6 with GHR mutations, 10 with clinically suspected Laron syndrome/GHIS, and 5 with GH gene deletion type 1A and anti-GH antibodies) [216]. Mean growth velocity increased from 3.1 cm/year pretreatment to 7.4 cm/year in year 1, 5.6 cm/year in year 2, and a range of 3.9–5 cm/year in years 3–12 of treatment. HtSDS compared to pretreatment values increased by a mean of +1.9 SD, and (near) AH achieved was a mean of 13.4 cm more than expected from their untreated trajectory on the Laron syndrome growth charts [216]. Although only 3 patients in this study reached a normal AH (greater than –2 SD), the severe phenotype of untreated adults, the significant increase in (near-) AH reported, the unanimous growth velocity acceleration compared to pretreatment values in multiple short-term studies, and the lack of an alternative treatment make IGF-I a strongly recommended treatment for growth failure in patients with PIGFD as diagnosed below.

7.2. Given the absence of a single "best" test that predicts responsiveness to GH treatment, we suggest basing the diagnosis of PIGFD/GH insensitivity syndrome (GHIS) on a combination of factors that fall into 4 stages: (Conditional recommendation, ●●●○)

1 Screening: auxological parameters and low IGF-I concentration
2 Causes of secondary IGF-I deficiency must be excluded, including under-nutrition, hepatic disease, and GHD
3 Circulating levels of GHBP: very low or undetectable levels suggest Laron syndrome/GHIS while normal levels are noninformative
4 IGF-I generation test and mutation analyses can be helpful, but have limitations

Diagnosing PIGFD/GHIS has important therapeutic implications; these patients are expected to require IGF-I treatment because their underlying defect would make them unresponsive to GH therapy. Unfortunately, a gold

standard test that predicts responsiveness to GH treatment is still lacking. Thus, we recommend basing the diagnosis of PIGFD/GHIS on a combination of factors that fall into 4 stages.

The first two stages investigate whether a patient with short stature could potentially fall into the PIGFD/GHIS category. Patients with PIGFD/GHIS exhibit postnatal linear growth failure, and depending on type of PIGFD, can have prenatal growth failure as well (IGF-I gene defects, IGFALS deficiency, and some patients with Laron syndrome/GHIS). Additional characteristic features, such as microcephaly, protruding forehead, saddle nose, small chin, and high-pitched voice, may raise clinical suspicion [212, 217]. Serum IGF-I concentrations must be abnormally low for age and gender. Causes of secondary IGF-I deficiency must be excluded. These include GHD (via GH provocative tests, as discussed above), undernutrition (via weight for length or BMI curves; a 3-day diet analysis may also be helpful), and hepatic disease (via history, physical examination, and liver function tests). Of note, subtle undernutrition, consisting of caloric restriction or reduced protein intake, may suffice to lower IGF-I production. Thus, if suspected, repeat measurement of serum IGF-I concentration following a period of nutritional intervention is a worthwhile diagnostic exercise.

The third stage involves measurement of circulating levels of GHBP because very low or undetectable levels suggest Laron syndrome/GHIS, the most common and prototypical condition within the severe PIGFD/GHIS category. GHBP is created by proteolytic cleavage of the extracellular GH-binding domain of the GHR, so that patients lacking GHBP also lack the extracellular domain of the GHR, without which they cannot respond to GH treatment. However, patients with Laron syndrome may occasionally have normal or high levels of GHBP should their GHR gene mutation occur in the exons that encode either the transmembrane or cytoplasmic domain [212, 218, 219]. Thus, normal GHBP levels are insufficient to exclude the diagnosis of Laron syndrome or postreceptor defects.

GHBP measurement has other diagnostic limitations. Testing the 14 subjects enrolled in NCGS with the diagnosis of ISS and low (less than –2 SD) levels of GHBP identified GHR mutations in only 4 [220]. GHBP levels were not predictive of responses to GH treatment among patients undergoing short stature evaluations who did not have overt Laron syndrome [221].

The fourth stage consists of tests to confirm the diagnosis of PIGFD/GHIS. Relative concentrations of IGF-I, IGFBP-3, and acid labile subunit may provide clues as to the location of the defect along the somatotropic axis. The rationale behind an IGF-I generation test seems straightforward; measuring the IGF-I (and, in some cases, IGFBP-3) rise upon a brief course (<10 days) of GH injections can categorize patients into those who produce an adequate IGF-I response to GH and those who do not, and thereby predict which patients would be expected to respond clinically or not to GH treatment. Unfortunately, multiple protocols have been proposed for the IGF-I generation test, including incorporating it into a greater clinical scoring system [222, 223], but a standard protocol with IGF-I cutoff levels that have high sensitivity and specificity has not been established. Protocols and cutoff points determined using IGF-I measured by radioimmunoassay [111, 202] may not be currently valid, as IGF-I assays currently available clinically (double-antibody assays and mass spectrometry) have different reference ranges. Additionally, discordant results were obtained when the test was repeated in the same subjects using the same laboratory [224]. A randomized, cross-over design compared IGF-I generation tests using two different GH doses (7 days each) with IGF-I measurements on days 5 and 8 of GH administration in 198 subjects who had either normal growth, Laron syndrome homozygous for the same GHR mutation, the heterozygous relatives of Laron subjects, or children with GHD or ISS [225]. IGF-I and IGFBP-3 measurements significantly correlated from one test to the other while the rise in IGF-I or IGFBP-3 correlated between the low- and high-dose GH for all subjects except the ISS group [225]. Both basal and stimulated IGF-I levels overlapped between subjects with GHD and Laron syndrome, with 6/23 subjects with GHD failing to adequately increase IGF-I and 5/22 subjects with Laron syndrome exceeding the threshold rise in stimulated IGF-I, thereby limiting the diagnostic value of the test [226].

An alternative to the IGF-I generation test is mutation analysis of the genes known to cause PIGFD/GHIS [reviewed in 227–229]. Mutation analysis of the GHR gene if the GHBP level is very low or undetectable is confirmatory for Laron syndrome/GHIS. However, availability of genetic testing is currently limited (in the USA), with few commercial or research laboratories offering the service [230]. It may become easier to diagnose PIGFD/GHIS within the next years as genetic testing is expected to become more available and less costly. Gene-specific testing will always be limited to the known causes of PIGFD/GHIS, while the advent of whole-exome sequencing may enable identification of novel genetic causes [231]. Genetic testing is desirable for individuals for whom diag-

nostic uncertainty is problematic, in order to better direct treatment.

7.3. We recommend a trial of GH therapy before initiating IGF-I for patients with unexplained IGF-I deficiency. Patients with hormone signaling defects known to be unresponsive to GH treatment can start directly on IGF-I replacement; these include patients with very low or undetectable levels of GHBP and/or proven GHR gene mutations known to be associated with Laron syndrome/GHIS, GH-neutralizing antibodies, *STAT5b* gene mutations, and *IGF1* gene deletion or mutation. (Strong recommendation, ●●○○)

Patients with hormone signaling defects unresponsive to GH treatment may be started on IGF-I as initial therapy; at present, these are associated with very low or undetectable levels of GHBP and/or *GHR* mutations known to cause Laron syndrome/GHIS, *GH1* gene deletion (GHD type 1A) with GH-neutralizing antibodies, *STAT5b* gene mutations, and *IGF1* gene deletion or mutation. Other patients diagnosed with PIGFD should start with a therapeutic trial of GH, which, if effective (i.e., in patients with only partial GH insensitivity [232, 233]), is preferable to IGF-I treatment for 4 reasons. Studies have shown that the growth response of patients with GHD to GH treatment exceeds the growth response of patients with PIGFD to IGF-I treatment, with first-year treatment growth velocities of 10–12 cm/year versus 8–9 cm/year, respectively [217, 234, 235]. The difference is hypothesized to result from IGF-I-independent actions of GH on the growth plate; whereas most of the effects of GH are mediated via IGF-I, IGF-I treatment cannot replace the direct actions of GH itself [235, 236]. The second reason involves patient convenience and adherence to therapy; GH is a once-daily subcutaneous injection, while IGF-I (in the USA) is administered as twice-daily subcutaneous injections. Thirdly, hypoglycemia is not a risk with GH therapy, as it is with IGF-I treatment [237]. Lastly, GH increases not only IGF-I levels, but levels of IGFBP-3 as well. This may make it more physiological than IGF-I therapy and, at least theoretically, may be favorable regarding cancer risk [238]. Patients with Kowarski syndrome have a mutation in the *GH1* gene causing expression of a bioactive GH; they present with low IGF-I levels, normal or slightly increased GH secretion, and short stature that is responsive to GH therapy [239, 240]. Patients with IGFALS defects do not respond well to either GH or IGF-I treatment. Despite profoundly low circulating concentrations of IGF-I, their growth failure is mild [241, 242].

7.4. We suggest an IGF-I dose of 80–120 μg/kg b.i.d. Similar short-term outcomes were seen with 80 and 120

μg, but published studies had limitations and there is no strong evidence supporting superiority of one dose over the other. (Conditional recommendation, ●●○○)

Technical Remark: Outside of the USA, IGF-I is also used at 150–180 μg/kg once daily.

Effect of IGF-I dosing on AH outcomes has not been studied systematically. A single report of adult or near-AH (defined as bone age at least 16 years for males and 14 for females) in 21 patients treated with IGF-I for a mean of 10 years (6 with GHR mutations, 10 with clinically suspected Laron syndrome/GHIS, and 5 with *GH1* gene deletion and anti-GH antibodies) showed increased growth velocity and HtSDS compared to pretreatment values and to the AH expected from their untreated trajectory on the Laron syndrome growth charts [216], as described in section 7.1. above. However, this was an open-label, uncontrolled study in which doses varied (began at 40 μg/kg b.i.d. and increased by 40 μg/kg increments every 2 weeks up to 120 μg/kg b.i.d., though some subjects received 40–80 μg/kg b.i.d. for several months and some received doses as high as 150 μg/kg b.i.d. during some of their pubertal years) and were further confounded by the administration of gonadotropin-releasing hormone agonist therapy in 9 subjects with normally timed puberty who wanted to prolong time for growth.

The majority of data on IGF-I dosing effects come from comparisons across studies (which were predominantly uncontrolled) and open-label descriptive studies reporting on-treatment growth velocity and HtSDS versus pretreatment values. Tabulations of data, usually as growth velocity by year on treatment by study, can be found in several papers [217, 237, 243, 244]. Doses generally fell into twice-daily regimens of 40–120 μg/kg/dose or once-daily dosing at 150–200 μg/kg. The twice-daily dosing regimen developed in response to a pharmacokinetic study of IGF-I that found faster IGF-I turnover in patients with Laron syndrome than in healthy volunteers [245]. However, the once-daily approach is still followed by some, claiming similar growth velocities and fewer side effects [243, 246].

While authors have used comparisons across studies to support their preferred dosing regimen, this approach is fraught with limitations that preclude determination of definitive recommendations. Most studies provided short-term outcomes only. While some patients embedded within several studies reached AH, the effect of dosing on AH was not studied systematically. Patients were heterogeneous across studies, differing in diagnoses and age at initiation of treatment, and different preparations of IGF-I were used. With PIGFD being such a rare entity,

there have been four main study groups (Israel, Ecuador, USA, and Europe), and many papers actually represent different time points or outcomes of the same subjects from other papers, such that some published data are redundant. All studies were open-label. Puberty was a potential confounder in two ways: some patients also received gonadotropin-releasing hormone agonist therapy, and many reached puberty within their respective studies. Despite this, Tanner staging was not reported even though the primary outcome was growth velocity. There may also be limitations from publication bias (unpublished results) and in generalizability of results (most subjects studied had Laron syndrome/GHIS, and optimal dosing may differ for other forms of PIGFD).

As stated in the guiding principles of this document, harm prevention was accorded the utmost importance in formulating the recommendations. A published trial directly compared 2- and 3-year outcomes of two commonly recommended IGF-I doses given to Ecuadorian patients homozygous for the same GHR mutation [234, 247]. Fourteen received 120 µg/kg b.i.d. while 7 received 80 µg/kg b.i.d. based on time of entry into the study (2 started high dose in a randomized, placebo-controlled study, but 1 dropped out and another had acromegalic changes, so was moved to the lower dose). While the two dosing arms produced similar increases in growth velocity and HtSDS, the higher dose group showed accelerated skeletal maturation in the third year, associated with increased percent body fat and adrenal growth [247]. These short-term results suggest that the higher dose not only costs more, but may compromise AH gains via accelerated skeletal maturation. The potential for increased side effects, albeit from a study with limitations, in the absence of hard evidence clearly supporting benefit of high versus lower IGF-I doses for increasing AH in patients with PIGFD/GHIS led us to conditionally suggest use of the lower dose. Well-designed, randomized trials are needed to determine the optimal IGF-I dose that best balances benefit and risk.

7.5. We recommend administration of IGF-I 20 min after a carbohydrate-containing meal or snack, and education of patients/families on the symptoms and risk of hypoglycemia associated with IGF-I treatment. (Strong recommendation, ●●●●)

Hypoglycemia has been reported as a side effect of IGF-I treatment in every study and is included in the package insert, citing an occurrence rate of 42% of patients during their course of therapy. Although most episodes were mild or moderate, severe hypoglycemic reactions including loss of consciousness and seizure also

have occurred. Thus, an important aspect of patient safety is the education of patients/families about the symptoms, risks, and management of hypoglycemia associated with IGF-I treatment. The risk can be mitigated by administration of IGF-I 20 min after carbohydrate-containing meals or snacks, withholding an IGF-I dose if the patient is not going to eat, and being more vigilant during intercurrent illnesses, including home glucometer use. While the risk of hypoglycemia has been attributed to the insulin-like actions of IGF-I (a notable difference from GH treatment, which decreases insulin sensitivity as described above in section 4.4), hypoglycemia also has been recognized as a common feature of Laron syndrome/GHIS itself (attributed to the profound loss of GH action) [212, 248, 249].

Other potential side effects of IGF-I treatment are similar to those of GH: intracranial hypertension, SCFE, and progression of scoliosis. Like GH, IGF-I treatment is contraindicated in patients with active malignancy. Additional potential side effects of IGF-I treatment include lymphoid tissue hypertrophy (i.e., enlargement of the tonsils and adenoids), hypersensitivity and allergic reactions, and reactions to the benzyl alcohol component of the diluent.

GH Treatment: Balance of Benefit, Risk, and Cost

Children with severe GHD clearly benefit from GH treatment, so much so that the benefits markedly outweigh any potential harms due to GH treatment. For children with ISS who do not have GHD, the benefits of achieving taller stature via GH treatment are uncertain and of a lesser magnitude than the treatment benefits experienced by children with GHD. The degree of psychosocial disability in children with ISS is not clear. Quality of life studies regarding the burden of short stature and the benefit of treating with GH have had mixed results, with some negating the widely held belief that short children and adults have lowered self-esteem and quality of life than their taller peers [250–253] and others showing improvement in these parameters with GH therapy and taller stature [253–255]. The topic of psychological outcomes of GH treatment for short stature is systematically reviewed elsewhere [256].

Accordingly, for ISS treatment decisions where potential benefits are limited and uncertain, even potential harms of small magnitude or low probability become important considerations, since children with ISS are healthy and will continue to be healthy without treatment. Long-

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term risks are unknown, but there are theoretical concerns regarding increased risk of cancer, cerebrovascular disease, and metabolic side effects of GH treatment. The SAGhE (Safety and Appropriateness of Growth hormone treatments in Europe) study showed an increase in overall mortality in the French subgroup of GH-treated patients with ISS, GHD and SGA; however, another subgroup from the Netherlands, Belgium, and Sweden did not demonstrate a difference in mortality in similar patients [136, 137, 155]. Further studies are needed to clarify the benefits and long-term risks of GH treatment in the ISS population. Potentially, the degree of physical and/or psychosocial disability that an individual child suffers due to short stature could be used to determine which children should receive GH therapy [257]. Those ISS patients with an extremely short AH prediction could be considered physically disabled in that it may be difficult for them to navigate a world built to accommodate much taller adults. For these children, even a small increase in AH may be a considerable benefit. For children whose height will be closer to the adult normal range, the benefit of GH therapy versus the risk and the high cost of treatment may be less acceptable.

Additionally, the high cost of GH therapy (USD 35,000–50,000 per inch of height gained) [258] is difficult to justify for those in whom it is unclear if there are benefits of treatment. In light of these considerations, treating patients with ISS requires careful evaluation and monitoring, with consideration of alternative treatments such as psychological counseling [211].

Growth-Promoting Treatment: Expansion of Use

As a consequence of FDA approval for GH treatment for ISS, short children who do not meet the criteria for ISS (i.e., children in this "short but not ISS" category) are now seeking GH therapy to augment their height. (This category excludes short children with non-ISS conditions such as Turner syndrome and SHOX haploinsufficiency.) Since many insurance companies do not cover GH therapy for this purpose, parents who choose this option have to pay out of pocket. While GH therapy may increase height in these children by up to several inches, no evidence exists that this additional height significantly improves their quality of life or provides any other benefit. Given the absence of any evidence of benefit, there is no justification to tolerate even small degrees of potential harm due to GH treatment for medical height enhancement. GH treatment poses some possible serious long-

term adverse events that are not acceptable risks in a healthy child with normal AH potential. Therefore, regardless of parents' ability to pay, GH treatment for height augmentation in children who do not fit the criteria of ISS should be discouraged [259].

Severe PIGFD as defined by the FDA and in this statement is a rare disorder. IGF-I treatment is indicated for PIGFD with both height and IGF-I levels below –3 SD. FDA approval for treatment with IGF-I included those children with IGF-I gene deletion or inactivating mutation, GHR gene mutation or postreceptor signal transduction defects, or GH-inactivating antibodies. Low IGF-I levels are commonly found in GHD, undernutrition, chronic glucocorticoid use, hypothyroidism, and chronic illness, all of which are conditions that are associated with slow growth. Therefore, low IGF-I concentrations and slow growth velocity alone are insufficient criteria to make the diagnosis of PIGFD. Treatment directed at the cause of secondary IGF-I deficiency should be sought, rather than IGF-I therapy. While some authors have suggested that many children with ISS have IGF-I deficiency, and would be better served if treated with IGF-I rather than GH, there are no data to support this hypothesis. In fact, treating a GH-sufficient child with IGF-I may suppress endogenous GH production, decrease production of IGF-I, and reduce delivery of GH to growing bone [260].

Better diagnostic tests are needed in order to more definitively determine which children have PIGFD and would be best served by treating with IGF-I rather than GH. For children who do not meet the FDA criteria for PIGFD, yet meet indications for GH therapy, an initial trial of GH can be used. The safety profile of IGF-I is similar to that of GH, but with the addition of hypoglycemia. This additional risk should be considered when deciding if IGF-I should be used as initial treatment when the diagnosis of PIGFD is suspected.

Conclusions and Future Directions

Careful review of the existing evidence revealed gaps in the knowledge base and areas open for future clinical investigation and treatment guideline development. Chief among the challenges is assessing the outcome of AH. Much of today's clinical practice is based on studies with short-term outcomes. The lack of tight correlation between short-term and long-term outcomes downgraded the reliability of such studies in accordance with the rigorous methodologies used in the creation of this docu-

ment. At the same time, while AH and other long-term outcomes are the benchmarks to be sought, we must acknowledge the logistical and cost challenges in conducting such long-term studies prospectively and the difficulties in correctly categorizing subjects and treatments in such long-term studies retrospectively.

Beyond duration of follow-up, the current knowledge base contains gaps that impede the clear definition and hence delivery of what is considered good clinical care. First and foremost is the need for improved diagnostics. This includes universal adoption of standardized IGF-I and GH assays and standards, and modification of current and/or development of new functional tests (GH provocative and IGF-I generation tests) that better distinguish patients into hormonally deficient versus sufficient. Genetic testing is expected to expand and offer additional insights, and elucidation of markers for therapeutic responsiveness may help guide clinical decisions. While current MRI technology is useful in identifying gross structural lesions, advances in imaging techniques will hopefully allow diagnosis of more subtle changes that correlate with clinical function.

In order to define quality care, complementing the need for better diagnostics is the need for better outcome metrics. Much of short stature treatment, including that aimed at the entire ISS category, is based on the supposition that taller stature will lead to improved quality of life. Designing and validating quality of life measures that appropriately assess this patient population, such as the QoLISSY instrument currently under development [261, 262], is only the first step in testing the underlying supposition and the effectiveness of treatment modalities. More reasoned and uniform therapeutic goals will aid in determining the appropriate endpoints for treatment clinically [263] and increase consistency across future research studies. Long-term safety data, i.e. effects in adults who had been treated during childhood, still need to be collected, a topic discussed in the position statement on GH Safety on behalf of the European Society for Pediatric Endocrinology, the GH Research Society, and the PES [264].

Meanwhile, the field is continuing to evolve. Newer therapeutics include bioequivalent GH products and a combined GH/IGF-I product [265]. The most sought-after intervention possibility continues to be an effective sustained-release GH preparation that will reduce the required frequency of injections [266, 267]. Likewise, some studies have suggested potential benefit of treating patients with GH who have non-FDA-approved indications, such as Crohn disease, cystic fibrosis, and gluco-

corticoid-dependent patients, and some have advocated further expanding the potential patient population by relaxing the height criteria for ISS and PIGFD; these topics are beyond the scope of this document to review.

Finally, in assessing the benefits, risks, and costs of GH and IGF-I treatments, both as a whole and for a given patient, one must take into account the availability of alternative therapies [268]. Growth-augmenting treatment options include oxandrolone, testosterone for boys with constitutional delay of growth and puberty (an indication for which GH is considered inappropriate), and analogs of gonadotropin-releasing hormone to delay puberty and experimentally with aromatase inhibitors, both aimed at delaying epiphyseal fusion. No treatment at all is also a very reasonable option, given that short stature per se is not a disease, and the relationship between AH and adult quality of life is weak and poorly understood. Psychological counseling should always be offered for patients suffering due to their stature, either in addition to or instead of hormone treatment as appropriate, although the efficacy of counseling for short stature has not been rigorously evaluated.

In conclusion, given the unanswered questions, the nuanced distinctions, and the dynamic status of the field, we recommend that only pediatric endocrinologists manage the evaluation for GHD-ISS-PIGFD and their treatment. We also recommend further study of the unresolved issues highlighted in these guidelines. In the meantime, we reiterate the importance of individualized patient care; lack of studies of sufficient quality in support of a practice is not the same as evidence against the practice, and interpatient variability means recommendations made at the group level may not be optimal for a particular individual patient.

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Disclosure Statement

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