

**AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND  
AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR  
MANAGEMENT OF GROWTH HORMONE DEFICIENCY IN ADULTS AND  
PATIENTS TRANSITIONING FROM PEDIATRIC TO ADULT CARE**

**2019 AAACE GROWTH HORMONE TASK FORCE**

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*This document represents the official position of the American Association of Clinical Endocrinologists and American College of Endocrinology. Where there were no randomized controlled trials or specific U.S. FDA labeling for issues in clinical practice, the participating clinical experts utilized their judgment and experience. Every effort was made to achieve consensus among the committee members. Position statements are meant to provide guidance, but they are not to be considered prescriptive for any individual patient and cannot replace the judgment of a clinician.*

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**ABSTRACT**

**Objective:** The development of these guidelines is sponsored by the American Association of Clinical Endocrinologists (AACE) Board of Directors and American College of Endocrinology (ACE) Board of Trustees and adheres with published AACE protocols for the standardized production of clinical practice guidelines (CPG).

**Methods:** Recommendations are based on diligent reviews of clinical evidence with transparent incorporation of subjective factors, according to established AACE/ACE guidelines for guidelines protocols.

**Results:** The Executive Summary of this 2019 updated guideline contains 58 numbered recommendations: 12 are Grade A (21%), 19 are Grade B (33%), 21 are Grade C (36%), and 6 are Grade D (10%). These detailed, evidence-based recommendations allow for nuance-based clinical decision-making that addresses multiple aspects of real-world care of patients. The evidence base presented in the subsequent Appendix provides relevant supporting information for the Executive Summary recommendations. This update contains 357 citations of which 51 (14%) are evidence level (EL) 1 (strong), 168 (47%) are EL 2 (intermediate), 61 (17%) are EL 3 (weak), and 77 (22%) are EL 4 (no clinical evidence).

**Conclusion:** This CPG is a practical tool that practicing endocrinologists and regulatory bodies can refer to regarding the identification, diagnosis, and treatment of adults and patients transitioning from pediatric to adult-care services with growth hormone deficiency (GHD). It provides guidelines on assessment, screening, diagnostic testing, and treatment recommendations for a range of individuals with various causes of adult GHD. The recommendations emphasize the importance of considering testing patients with a reasonable level of clinical suspicion of GHD using appropriate growth hormone (GH) cut-points for various GH-stimulation tests to accurately diagnose adult GHD, and to exercise caution interpreting serum GH and insulin-like growth factor-1 (IGF-1) levels, as various GH and IGF-1 assays are used to support treatment decisions. The intention to treat often requires sound clinical judgment and careful assessment of the benefits and risks specific to each individual patient. Unapproved uses of GH, long-term safety, and the current status of long-acting GH preparations are also discussed in this document. (*Endocr Pract.* 2019;25:1191-1232)

**LAY ABSTRACT**

This updated guideline provides evidence-based recommendations regarding the identification, screening, assessment, diagnosis, and treatment for a range of individuals with various causes of adult growth-hormone deficiency (GHD) and patients with childhood-onset GHD transitioning to adult care. The update summarizes the most current knowledge about the accuracy of available

GH-stimulation tests, safety of recombinant human GH (rhGH) replacement, unapproved uses of rhGH related to sports and aging, and new developments such as long-acting GH preparations that use a variety of technologies to prolong GH action. Recommendations offer a framework for physicians to manage patients with GHD effectively during transition to adult care and adulthood. Establishing a correct diagnosis is essential before consideration of replacement therapy with rhGH. Since the diagnosis of GHD in adults can be challenging, GH-stimulation tests are recommended based on individual patient circumstances and use of appropriate GH cut-points. Available GH-stimulation tests are discussed regarding variability, accuracy, reproducibility, safety, and contraindications, among other factors. The regimen for starting and maintaining rhGH treatment now uses individualized dose adjustments, which has improved effectiveness and reduced reported side effects, dependent on age, gender, body mass index, and various other individual characteristics. With careful dosing of rhGH replacement, many features of adult GHD are reversible and side effects of therapy can be minimized. Scientific studies have consistently shown rhGH therapy to be beneficial for adults with GHD, including improvements in body composition and quality of life, and have demonstrated the safety of short- and long-term rhGH replacement.

**Abbreviations:**

**AACE** = American Association of Clinical Endocrinologists; **ACE** = American College of Endocrinology; **AHSG** = alpha-2-HS-glycoprotein; **AO-GHD** = adult-onset growth hormone deficiency; **ARG** = arginine; **BEL** = best evidence level; **BMD** = bone mineral density; **BMI** = body mass index; **CI** = confidence interval; **CO-GHD** = childhood-onset growth hormone deficiency; **CPG** = clinical practice guideline; **CRP** = C-reactive protein; **DM** = diabetes mellitus; **DXA** = dual-energy X-ray absorptiometry; **EL** = evidence level; **FDA** = Food and Drug Administration; **FD-GST** = fixed-dose glucagon stimulation test; **GeNeSIS** = Genetics and Neuroendocrinology of Short Stature International Study; **GH** = growth hormone; **GHD** = growth hormone deficiency; **GHRH** = growth hormone-releasing hormone; **GST** = glucagon stimulation test; **HDL** = high-density lipoprotein; **HypoCCS** = Hypopituitary Control and Complications Study; **IGF-1** = insulin-like growth factor-1; **IGFBP** = insulin-like growth factor-binding protein; **IGHD** = isolated growth hormone deficiency; **ITT** = insulin tolerance test; **KIMS** = Kabi International Metabolic Surveillance; **LAGH** = long-acting growth hormone; **LDL** = low-density lipoprotein; **LIF** = leukemia inhibitory factor; **MPHD** = multiple pituitary hormone deficiencies; **MRI** = magnetic resonance imaging; **P-III-NP** = procollagen

type-III amino-terminal pro-peptide; **PHD** = pituitary hormone deficiencies; **QoL** = quality of life; **rhGH** = recombinant human growth hormone; **ROC** = receiver operating characteristic; **RR** = relative risk; **SAH** = subarachnoid hemorrhage; **SDS** = standard deviation score; **SIR** = standardized incidence ratio; **SN** = secondary neoplasms; **T3** = triiodothyronine; **TBI** = traumatic brain injury; **VDBP** = vitamin D-binding protein; **WADA** = World Anti-Doping Agency; **WB-GST** = weight-based glucagon stimulation test

## INTRODUCTION

Adult growth hormone deficiency (GHD) results from decreased growth hormone (GH) secretion from the anterior pituitary gland that is more pronounced than the physiologic decline of the growth hormone–releasing hormone (GHRH)-GH-insulin-like growth factor-1 (IGF-1) axis associated with aging. This clinical entity is associated with numerous adverse metabolic abnormalities (1-3). Furthermore, it is likely, although not definitively proven, that adult GHD per se contributes to increased cardiovascular morbidity and mortality that has been observed in patients with a variety of pituitary disorders compared to the general population (4-8).

In a patient where the clinician is suspicious of adult GHD, establishing the diagnosis is essential before replacement therapy with recombinant human GH (rhGH) can be considered. In 1985, rhGH first became commercially available in the United States (U.S.), and since then, there is now accumulating evidence of its beneficial effects in reversing many (9-29), but not all (30-32), of the metabolic abnormalities associated with this condition. Nonetheless, there is still some controversy in the U.S. regarding the appropriate use of rhGH therapy in adults with GHD, largely stemming from a combination of factors that include the high cost of therapy (rhGH costs approximately \$18,000 to \$30,000 per year depending on the dose and brand used) (33), need to administer daily injections which can be burdensome for some patients and caregivers, lack of awareness among some clinicians regarding the indications and benefits of rhGH in adults, difficulty to safely conduct GH–stimulation tests in physician offices, and concerns about whether there are adverse effects after long-term therapy. In addition, there is still a misconception by some regarding the difference between true adult GHD (i.e., lower GH secretion than normal for the appropriate age and sex due to acquired and genetic causes) versus the physiologic decline in endogenous GH secretion due to aging, and the continued inappropriate and unapproved use of rhGH in nonmedical conditions (i.e., sports and aging).

The benefits and utilization of rhGH replacement therapy in adults and young patients transitioning from

pediatric to adult-care services (herein referred to as “transition” patients) with GHD have previously been detailed by the American Association of Clinical Endocrinologists (AACE), with its clinical practice guideline (CPG) first published in 2009 (34). Since then, several recent studies have further demonstrated the safety of long-term rhGH replacement in adults with GHD (6,35-38), but whether long-term rhGH treatment improves outcomes such as cardiovascular mortality and fracture rates remains to be fully established. On the other hand, the incidence of diabetes mellitus (DM) in adults on long-term rhGH therapy has been shown to be increased in some studies (39,40), while others have not observed any change after long-term treatment (30,41). Furthermore, even after over 20 years of rhGH replacement aimed at normalizing serum IGF-1 levels in adults with GHD, there are no robust data to suggest that the risk of cancer, secondary neoplasms (SN) and hypothalamic-pituitary tumor recurrence is increased, although it remains possible that a longer period of follow-up may still be needed to discern any small increases in these risks.

Early studies utilized rhGH doses in replacement regimens that took into consideration of body weight or body surface area, and dose adjustments were based on body composition outcomes, analogous to pediatric practice (42-44), but side effects were frequently observed that were mainly due to the fluid-retaining effects of rhGH. In light of these observations, rhGH treatment regimens now use dose-titration strategies targeting serum IGF-1 normalization to account for interindividual differences in GH sensitivity that takes into consideration age, gender, body mass index (BMI), and various other baseline characteristics (45-47). The utilization of individualized, stepwise dose adjustments based on serum IGF-1 levels has resulted in improved treatment efficacy, provided the patient is treatment-adherent, and reductions in reported side effects (48,49).

Adult GHD is most often associated with damage to the hypothalamic-pituitary region as a result of tumors, and/or treatment with surgery and radiation (50). Nonetheless, in the past decade, several other subpopulations of patients, such as those with traumatic brain injury (TBI), subarachnoid hemorrhage, ischemic stroke, and infections in the central nervous system, have been described to be at risk for developing adult GHD. For these patients, clinicians may be required to consider undertaking further biochemical testing to assess for adult GHD (51,52). However, the diagnostic accuracy and reliability of currently available GH–stimulation tests in these groups of patients have not been adequately studied. Clinicians are therefore now faced with the possibility of assessing these patient populations, where neither testing nor long-term treatment efficacy has been evaluated extensively in large sample sizes.

The purpose of this update to the 2009 AACE adult GHD CPG (34) is to summarize current knowledge about the accuracy of available GH–stimulation tests, hetero-

generality of commercially available GH and IGF-1 assays, safety of rhGH replacement, misuse of rhGH in sports and aging, and new developments in this field. In this CPG, evidence-based practical recommendations are offered as a framework to clinicians for better and effective management of patients with GHD transitioning from pediatric to adult-care services and into adulthood.

## METHODS

This CPG was developed in accordance with the 2017 AACE Protocol for Standardized Production of Clinical Practice Guidelines (53), whereby AACE and the American College of Endocrinology (ACE) have updated the workflow for clinical practice tools to prioritize clinical problem-solving and management (Fig. 1). The 2017 AACE/ACE CPG production strategy began with an environmental scan of the disease “space” to identify the most relevant clinical problems and needs facing the clinical endocrinologist (e.g., diagnosis of adult GHD or treatment of adult GHD in elderly patients and those with a distant history of cancer). This updated CPG methodology provides a framework for patient-first language, greater detail for evidence ratings, and structure for the involvement of the American College of Endocrinology Scientific Referencing Subcommittee, a dedicated resource for the rating of evidence, mapping of grades, and general oversight of the entire CPG production process. A critical improvement in the 2017 AACE/ACE CPG production strategy is to create documents that are

easier to use and less cumbersome. Nevertheless, as with all white papers and increasing diligence on the part of the writing team, it is inevitable that an element of subjectivity will be encountered in certain areas and clinical discretion must be recognized by the reader when interpreting the information.

Reference citations in the text of this document include the reference number, and numerical (evidence level [EL] 1 to 4), semantic, and methodology descriptors (Table 1) (53). All primary writers have made disclosures regarding multiplicities of interests and have attested that they are not employed by industry. In addition, all primary writers are current good-standing AACE members and credentialed experts in this field. Primary writers submitted contributions to specific clinical questions, which were subsequently reviewed, discussed, and integrated into the final document. This input provides the basis for the recommendations herein. The format of this CPG is based upon specific and relevant clinical questions.

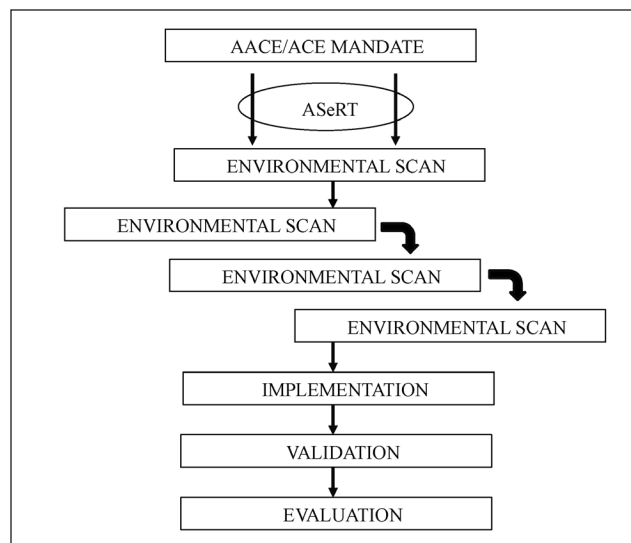
Recommendations (labeled “R”) are assigned grades that map to the best evidence level (BEL) ratings based on the highest quality supporting EL (Table 1), evidence analysis, and subjective factors (Table 2) (53), all of which have been rated based on recommendation qualifiers (Table 3) (53). The EL of scientific substantiation, specific EL subjective factors (for individual citations), recommendation qualifiers (for aggregate evidence base for an individual recommendation), and EL to recommendation grade mapping have been more clearly delineated for transparency, allowing for more interpretative flexibility (Tables 1 to 4) (53). Details regarding each recommendation may be found in the upcoming corresponding section of the CPG Evidence Base Appendix that includes a complete list of supporting references. Thus, the process leading to a final recommendation and grade is not rigid, but rather incorporates complex expert integration of objective and subjective factors meant to reflect optimal real-life clinical decision-making, options, and individualization of care. This document is a guideline; since individual circumstances and clinical presentations differ from patient to patient, ultimate clinical management is based on what is in the best interest of the patient that would also involve the patient’s input (“patient-centered care”) and reasonable clinical judgment by the treating clinician.

This CPG was extensively reviewed and approved by all of the primary writers, other invited experts, the AACE Publications Committee, the AACE Board of Directors, and the ACE Board of Trustees before submission for peer review by *Endocrine Practice*.

## EXECUTIVE SUMMARY

### Q1. WHAT IS ADULT GHD?

**R1.** The clinician should consider the possibility of



**Fig. 1.** 2017 AACE/ACE CPG Production Strategy. Current AACE CPG prioritizes real-world clinical problem solving by first determining key issues to be examined, then creating a pragmatic CPA approach, and then providing the problem-oriented scientific substantiation in the form of focused CPA-driven CPG and patient safety CC. This is followed by implementation and validation strategies and after a CPG is validated, there will be an evaluation step. *AACE* = American Association of Clinical Endocrinologists; *ACE* = American College of Endocrinology; *ASeRT* = ACE Scientific Referencing Team; *CC* = clinical checklist; *CPA* = clinical practice algorithm; *CPG* = clinical practice guidelines.



adult GHD in each individual patient with a history of hypothalamic-pituitary disease, as this condition is a well-defined clinical entity that is associated with excess morbidity and mortality (**Grade B; BEL 2**).

**R2.** The clinician should be aware that adults can be diagnosed with GHD in childhood (childhood-onset

GHD [CO-GHD]) and adulthood (adult-onset GHD [AO-GHD]) (**Grade B; BEL 2**).

**R3.** The most common causes of CO-GHD and AO-GHD are isolated idiopathic GHD and hypothalamic-pituitary tumors and/or their treatment regimens, respectively; hence, the possibility of GHD should

Table 1 2017 American Association of Clinical Endocrinologists Protocol of Clinical Practice Guidelines - Step I Evidence Rating <sup>a</sup>		
Numerical descriptor <sup>b</sup>	Semantic descriptor	Methodology descriptor
<b>STRONG EVIDENCE</b>		
1 (1)	RCT	Randomized controlled trial <sup>c</sup>
1 (1)	MRCT	Meta-analysis of only randomized controlled trials
<b>INTERMEDIATE EVIDENCE</b>		
2 (2)	MNRCT	Meta-analysis including nonrandomized prospective or case-controlled trials
2 (new)	NMA	Network meta-analysis
2 (2)	NRCT	Nonrandomized controlled trial (or unconfirmed randomization)
2 (2)	PCS	Prospective cohort study (does not include open-label extension study)
2 (2)	RCCS	Retrospective case-control study
2 (new)	NCCS	Nested case-control study
2 (3; reassigned)	CSS	Cross-sectional study
2 (3; reassigned)	ES	Epidemiologic study (hypothesis driven; includes survey, registry, data-mining, with or without retrospective uni-multivariate analyses or propensity matching)
2 (new)	OLES	Open-label extension study
2 (new)	PHAS	Post-hoc analysis study
<b>WEAK EVIDENCE</b>		
3 (new)	DS	Discovery science (explorative/inductive; includes -omics, "big data," network analysis, systems biology, Bayesian inference, modeling)
3 (new)	ECON	Economic study (includes Markov models, pharmaco-economics)
3 (3)	CCS	Consecutive case series (N >1)
3 (3)	SCR	Since case report (N = 1)
3 (new)	PRECLIN	Preclinical study (e.g., feasibility, safety)
3 (new)	BR	Basic research (must be high impact and relevant)
<b>NO EVIDENCE</b>		
4 (4)	NE	No evidence (theory, opinion, consensus, review, position, policy, guideline)
4 (new)	O	Other (e.g., lower impact/relevant basic research; any highly flawed study)
Abbreviations: BR = basic research; CCS = consecutive case series; CSS = cross-sectional study; DS = discovery science; ECON = economic study; ES = epidemiologic study; MNRCT = meta-analysis including nonrandomized prospective or case-controlled trials; MRCT = meta-analysis of only randomized controlled trials; NCCS = nested case-control study; NE = no evidence; NMA = network meta-analysis; NRCT = nonrandomized controlled trial; O = other; OLES = open-label extension study; PCS = prospective cohort study; PHAS = post-hoc analysis study; PRECLIN = preclinical study; RCCS = retrospective case-control study; RCT = randomized controlled trial; SCR = since case report.		
<sup>a</sup> Based on the principle that interventions, scientific control, generalizability, methodologic flaws, and evidentiary details determine strength, consistent with other evidence-based methodology systems. Numerical and semantic descriptors of evidence levels provided in on-line supplementary material.		
<sup>b</sup> The original numerical description from Guidelines for Guidelines, Algorithms, and Checklists 2004, 2010, and 2014 are provided in parentheses.		
<sup>c</sup> The superiority of randomized controlled trials over all other studies, and in particular meta-analysis of randomized controlled trials, is discussed in reference (53). Meta-analysis of randomized controlled trials is inferior to randomized controlled trials due to the bias introduced by being a retrospective analysis.		
Reprinted with permission from Mechanick et al (53).		

<b>Table 2</b> <b>2017 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines - Step II: Evidence Analysis and Subjective Factors<sup>a</sup></b>		
Study design <sup>a</sup>	Data analysis <sup>b</sup>	Interpretation of results
Allocation concealment (randomization)	Intent-to-treat	Generalizability
Blinding <sup>c</sup>	Modeling (e.g., Markov)	Incompleteness
Comparator group	Network analysis	Logical
Endpoints (real clinical versus surrogate)	Statistics	Overstated
Hypothesis	Appropriate follow-up	Validity
Power analysis (too small sample size)	Appropriate trial termination	
Premise		
Type 1 error (e.g., adjusted for PHAS)		
Abbreviation: PHAS = post hoc analysis study. <sup>a</sup> These subjective factors pertain to an individual citation. Subjective factors are provided in online supplementary material from Mechanick et al (53). <sup>b</sup> Are these elements appropriate for the given study? <sup>c</sup> Including patients, clinicians, data collectors, adjudicators of outcome, and data analysts. Reprinted with permission from Mechanick et al (53).		

<b>Table 3</b> <b>2017 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines - Step III: Recommendation Qualifiers<sup>a</sup></b>
Cascades (are there other recommendation versions based on ethnocultural factors?)
Dissenting opinions (based on HCP and patient preferences)
Economic (e.g., cost-effectiveness, cost-benefit, value)
Evidence Base (are there significant gaps or is there overwhelming evidence?)
Relevance (patient-oriented evidence that matters versus disease-oriented evidence; social acceptability)
Resource availability (limited or sufficient)
Risk to benefit
Abbreviation: HCP = healthcare professional. <sup>a</sup> Each of these elements pertains to the recommendation statement with the evidence considered in aggregate. The element may be positive or negative, and therefore modify a final recommendation grade. Recommendation qualifiers are provided in online supplementary material from Mechanick et al (53). Reprinted with permission from Mechanick et al (53).

be considered in these patients (**Grade B; based primarily on expert opinion of the committee**). **R4.** Several nontumoral causes of adult GHD (e.g., TBI, subarachnoid hemorrhage, ischemic stroke, and infections in the central nervous system) have been increasingly described in the past decade, and screening may be considered although the accuracy and reliability of GH-stimulation tests for the diagnosis of adult GHD have not been studied extensively in these populations (**Grade C; BEL 2**).

**Q2. ARE THERE ANY DIFFERENCES BETWEEN CO-GHD VERSUS AO-GHD?**

**R5.** It is recommended that clinicians recognize the differences in the etiology of CO-GHD versus AO-GHD as there are differences in the phenotypic

features which are due to the fact that CO-GHD occurs during the developmental years and that adults with CO-GHD may have had a longer duration of being GH-deficient than their AO-GHD counterparts (**Grade A; BEL 1**).

**Q3. HOW SHOULD PEDIATRIC PATIENTS WITH CO-GHD BE TRANSITIONED TO ADULT-CARE SERVICES?**

**R6.** Transition is a vulnerable period when adolescents may drop out of follow-up medical care. Pediatricians should start counseling patients and caregivers early about the potential of future transition and collaborate closely with adult endocrinologists closer to the time to facilitate a seamless transition to adult endocrine-care services (**Grade C; BEL 2**).

**Table 4**  
**2017 American Association of Clinical Endocrinologists Protocol for**  
**Production of Clinical Practice Guidelines: Step IV - Grading of Recommendations;**  
**How Different Evidence Levels Can Be Mapped to the Same Recommendation Grade<sup>a</sup>**

Best Evidence Level	Predominantly negative SF and/or RQ	Predominantly positive SF and/or RQ	Consensus for recommendation and for Grade	EL to grade mapping	Map to final recommendation grade
1	No	No	>66%	Direct	1 → A
Any <sup>b</sup>	No	No	100%	Rule	Any → A (new)
2	No	Yes	>66%	Adjust up	2 → A
2	No	No	>66%	Direct	2 → B
1	Yes	No	>66%	Adjust down	1 → B
3	No	Yes	>66%	Adjust up	3 → B
3	No	No	>66%	Direct	3 → C
2	Yes	No	>66%	Adjust down	2 → C
4	No	Yes	>66%	Adjust up	4 → C
4	No	No	>66%	Direct	4 → D
3	Yes	No	>66%	Adjust down	3 → D
Any <sup>b</sup>	Yes/no	Yes/no	>66%	Rule	Any → AD (new)

Abbreviations: EL = evidence level; RQ = recommendation qualifiers; SF = subjective factors.

<sup>a</sup>Recommendation Grade A = “very strong;” B = “strong;” C = “not strong;” D = “primarily based on expert opinion.” Mappings are provided in online supplementary material from Mechanick et al (53).

<sup>b</sup>Rule-based adjustment wherein any recommendation can be a “very strong” Grade A if there is 100% consensus to use this designation. Similarly, if >66% consensus is not reached, even with some degree of scientific substantiation, a “primarily based on expert opinion” Grade D designation is assigned. The reasons for downgrading to D may be an inconclusive or inconsistent evidence base or simply failure of the expert writing committee to sufficiently agree. Note that any formulated recommendation is omitted from the document if sufficiently flawed, so any Grade D recommendation in the final document must be deemed sufficiently important.

Rule-based adjustments are provided in online supplementary material from Mechanick et al (53).

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#### Q4. WHAT ARE THE BENEFITS OF CONTINUING rhGH REPLACEMENT IN TRANSITION PATIENTS WITH CO-GHD?

**R7.** It is recommended that adults with CO-GHD caused by structural pituitary or brain tumors be followed up closely during transition as these patients tend to have lower bone mineral density, impaired bone microarchitecture, and more adverse body composition abnormalities and cardiovascular risk markers than those with AO-GHD (**Grade A; BEL 1**).

**R8.** Resuming rhGH replacement therapy in patients with confirmed persistent GHD during the transition period after achievement of final height is recommended, as most studies have reported long-term improvement in body composition, bone health, quality of life, and lipid metabolism in adulthood (**Grade A; BEL 1**).

#### Q5. WHO SHOULD BE TESTED FOR ADULT GHD?

**R9.** GH-stimulation test/s should only be performed based on the appropriate clinical context of each indi-

vidual patient with a history suggestive of a reasonable clinical suspicion of GHD, and with the intent to initiate rhGH replacement if the diagnosis is confirmed (**Grade D; based on expert opinion**).

**R10.** The diagnosis of adult GHD can be made without the need for performing GH-stimulation testing in certain patient subtypes, such as patients with organic hypothalamic-pituitary disease (e.g., suprasellar mass with previous surgery and cranial irradiation) and biochemical evidence of multiple pituitary hormone deficiencies (MPHD) (≥3 pituitary hormone deficiencies [PHD]) together with low-serum IGF-1 levels (< -2.0 standard deviation score [SDS]), genetic defects affecting the hypothalamic-pituitary axes, and hypothalamic-pituitary structural brain defects (**Grade C; BEL 3**).

**R11.** In patients with ≤2 PHD, low-serum IGF-1 levels (< -2.0 SDS) alone are not sufficient to make a diagnosis of adult GHD; clinicians should perform 1 GH-stimulation test to confirm the diagnosis (**Grade B; BEL 4; upgraded by consensus based on expert opinion**).

**R12.** After longitudinal growth is completed in transi-

tion patients with idiopathic isolated GHD, those with low-normal (between 0 to  $-2$  SDS) or low ( $< -2$  SDS) serum IGF-1 levels should be retested for GHD with GH-stimulation tests after at least 1 month following discontinuation of rhGH therapy (**Grade B; BEL 4; upgraded by consensus based on expert opinion**).

**R13.** After longitudinal growth is completed in transition patients with isolated GHD (IGHD) and the presence of organic hypothalamic-pituitary disease (e.g., craniopharyngioma, pituitary hypoplasia, ectopic posterior pituitary, or previous cranial irradiation), the number of GH-stimulation tests to be undertaken should be guided by the degree of clinical suspicion for GHD. If clinical suspicion is high, 1 GH-stimulation test is sufficient, but if clinical suspicion is low, then a second GH-stimulation test should be performed (**Grade B; BEL 4; upgraded by consensus based on expert opinion**).

**R14.** To continue rhGH replacement in adulthood, retesting for GHD with GH-stimulation test/s is recommended in most transition patients, especially patients with idiopathic isolated GHD and serum IGF-1 SDS  $< 0$ , when longitudinal growth is complete, and at least 1 month after discontinuation of pediatric rhGH therapy (**Grade A; BEL 1**).

**R15.** Patients with idiopathic IGHD and serum IGF-1  $\geq 0$  SDS are likely to have a normal GH-stimulation test; hence, retesting and rhGH therapy in these patients after completion of longitudinal growth are not required (**Grade C; BEL 2; downgraded due to inconsistent results**).

**R16.** Retesting is not required in transition patients with MPHD ( $\geq 3$  PHD) and low-serum IGF-1 levels ( $< -2.0$  SDS), patients with genetic defects affecting the hypothalamic-pituitary axes, and patients with hypothalamic-pituitary structural brain defects, and rhGH therapy may be continued in these patients without interruption (**Grade C; BEL 2; downgraded due to inconsistent results**).

**R17.** The risk for development of persistent GHD after radiation therapy is increased with higher radiation doses and longer duration of time since the therapy. Retesting those patients who initially test as GH-sufficient may be performed later in the transition period or in adulthood to rule out delayed GHD (**Grade B; BEL 2**).

**R18.** TBI and subarachnoid hemorrhage are now recognized clinical conditions that may cause GHD, but because GHD may be transient in these patients, GH-stimulation testing should be performed only after at least 12 months following the event (**Grade B; BEL 2**).

## Q6. HOW SHOULD ONE TEST FOR ADULT GHD?

**R19.** Random serum GH and IGF-1 levels cannot be used alone to make the diagnosis of adult GHD, and GH-stimulation test/s should be performed to confirm the diagnosis with the exception of certain subpopulations, such as patients with organic hypothalamic-pituitary disease (e.g., suprasellar mass with previous surgery and cranial irradiation) who have MPHD ( $\geq 3$  PHD) and low serum IGF-1 levels ( $< -2.0$  SDS), patients with genetic defects affecting the hypothalamic-pituitary axes, and patients with hypothalamic-pituitary structural brain defects (**Grade B; BEL 4; upgraded by consensus based on expert opinion**).

**R20.** GH-stimulation tests should only be performed after all other PHD have been optimally replaced with stable hormone replacement doses (**Grade C; BEL 4; upgraded by consensus based on expert opinion**).

**R21.** The insulin tolerance test (ITT) remains the gold-standard test to establish the diagnosis of adult GHD using a peak GH cut-point of  $5 \mu\text{g/L}$ . However, this test is increasingly used less frequently in the U.S. because of safety concerns, laboriousness, potential to cause severe hypoglycemia, and contraindicated in certain patients, such as elderly patients and those with seizure disorders and cardio/cerebrovascular disease. For adults suspected to have GHD and if the ITT is contraindicated or is not feasible to be performed in these patients, the glucagon-stimulation test (GST) and the macimorelin test could be considered as alternative tests (**Grade B; BEL 1**).

**R22.** For the GST, we recommend utilizing BMI-appropriate GH cut-points to diagnose adult GHD to reduce the possibility of misclassifying GH-sufficient patients because increased BMI is associated with decreased glucagon-induced GH stimulatory effect. We recommend using the GH cut-point of  $3 \mu\text{g/L}$  for normal-weight (BMI  $< 25 \text{ kg/m}^2$ ) and overweight (BMI 25 to  $30 \text{ kg/m}^2$ ) patients with a high pretest probability, and a lower GH cut-point of  $1 \mu\text{g/L}$  for obese (BMI  $> 30 \text{ kg/m}^2$ ) and overweight (BMI 25 to  $30 \text{ kg/m}^2$ ) patients with a low pretest probability. In patients with glucose intolerance, the diagnostic accuracy of the GST remains unclear (**Grade B; BEL 2**).

**R23.** For the macimorelin-stimulation test, the U.S. Food and Drug Administration (FDA) approved this test for use as a diagnostic test for adult GHD in December, 2017, and selected the GH cut-point of  $2.8 \mu\text{g/L}$  to differentiate patients with normal GH secretion from those with GHD. However, it is not yet known whether BMI-adjusted peak GH cut-points for this test are needed for overweight and obese patients (**Grade B; BEL 2**).



**R24.** For transition patients, a feasible and validated GH-stimulation test has been less well studied. In this patient population, the ITT (using a GH cut-point  $\leq 5.0$   $\mu\text{g/L}$ ) may be utilized, but if the test is contraindicated or not feasible to be performed, the GST (using a GH cut-point of 3  $\mu\text{g/L}$  for normal-weight [BMI  $< 25$   $\text{kg/m}^2$ ] patients and overweight [BMI 25 to 30  $\text{kg/m}^2$ ] patients with a high pretest probability, and a lower GH cut-point of 1  $\mu\text{g/L}$  for overweight [BMI 25 to 30  $\text{kg/m}^2$ ] patients with a low pretest probability and obese [BMI  $> 30$   $\text{kg/m}^2$ ] patients) and the macimorelin test (using a GH cut-point  $\leq 2.8$   $\text{mg/L}$ ) can be considered as alternative tests (**Grade C; BEL 2**).

**R25.** Arginine (ARG) and levodopa (L-DOPA) testing have not been systematically evaluated and validated, and because these tests have low sensitivity and specificity in adults and transition patients with suspected GHD, we do not recommend utilizing these tests (**Grade B; BEL 2**).

#### **Q7. WHY ARE STANDARDIZED GH AND IGF-1 ASSAYS IMPORTANT IN THE MANAGEMENT OF ADULT GHD?**

**R26.** Substantial heterogeneity exists among currently utilized assays due to different standard preparations for calibration of GH immunoassays and lack of harmonization between various GH assays. It is recommended that laboratories adopt the standards set by the National Institute for Biological Standards and Control and state their methodology of analyses, including reporting serum GH levels in mass units without reliance of conversion factors (**Grade C; BEL 4; upgraded by consensus based on expert opinion**).

**R27.** It is suggested that all assay manufacturers indicate the validation of their assay, including specification of the GH isoforms detected, analyte being measured, specificities of the antibodies used, and presence or absence of GH-binding protein interference (**Grade C; BEL 4; upgraded by consensus based on expert opinion**).

**R28.** Differences in serum IGF-1 assay performance should be considered when evaluating and monitoring rhGH therapy in adults with GHD, and, if possible, the same IGF-1 assay should be used for a given patient throughout evaluation for diagnosis and follow-up (**Grade C; BEL 4; upgraded by consensus based on expert opinion**).

**R29.** Quality-control materials should be used, widely verified, and disseminated among laboratories for uniformity (**Grade C; BEL 4; upgraded by consensus based on expert opinion**).

**R30.** Because certain conditions such as DM, malnutrition, chronic liver disease, and renal diseases

may lower serum IGF-1 levels that may not be due to GHD, reliable sera from healthy subjects and from such patients should be employed for validation of the assays (**Grade C; BEL 4**).

**R31.** Normative IGF-1 assay data should be provided by each laboratory and should include a sufficient random sample of individuals from a wide range of ages to achieve clinical efficacy and minimize the induction of side effects (**Grade C; BEL 4; upgraded by consensus based on expert opinion**).

**R32.** Laboratories, in addition to reporting serum IGF-1 levels, should report IGF-1 SDS values (Z-scores) (**Grade C; BEL 4; upgraded by consensus based on expert opinion**).

#### **Q8. HOW SHOULD INITIATION AND MONITORING OF rhGH REPLACEMENT BE UNDERTAKEN?**

**R33.** The use of one commercial rhGH product is not suggested over another, as there is no evidence that one rhGH product is more advantageous than another (**Grade D**).

**R34.** It is recommended to use serum IGF-1 as the biomarker for guiding rhGH dose adjustments (**Grade A; BEL 1**).

**R35.** It is recommended to individualize rhGH dosing independent of body weight, starting with a low dose, and gradually up-titrating the dose to normalize serum IGF-1 levels with the primary aim of minimizing the induction of side effects (**Grade A; BEL 1**).

**R36.** Serum IGF-1 levels should be targeted within the age-adjusted reference range (IGF-1 SDS between  $-2$  and  $+2$ ) provided by the laboratory utilized. This decision should consider the pretreatment IGF-1 SDS and the circumstances and tolerability of each individual patient. Because some patients may only tolerate lower rhGH doses frequently limited by side effects, whereas others may require higher rhGH doses to achieve desired clinical effects, the goals of treatment should be the clinical response, avoidance of side effects, and targeting serum IGF-1 levels to fall within the age-adjusted reference range (IGF-1 SDS between  $-2$  and  $+2$ ) (**Grade D; based on expert opinion of the committee**).

**R37.** It is recommended to initiate rhGH therapy using low GH dosages (0.1 to 0.2  $\text{mg/day}$ ) in GH-deficient patients with concurrent DM, obesity, older age, and previous gestational DM to avoid impairment of glucose metabolism. Higher rhGH starting doses (0.3 to 0.4  $\text{mg/day}$ ) are advised in nondiabetic young adults  $< 30$  years of age and women on oral estrogen therapy (**Grade A; BEL 1**).

**R38.** After starting on rhGH therapy, it is recommended to follow patients at 1- to 2-month intervals

initially, increasing the rhGH dose in increments of 0.1 to 0.2 mg/day based on the clinical response, serum IGF-1 levels, side effects, and individual considerations. Once maintenance doses are achieved, follow-up can be implemented at approximately 6- to 12-month intervals. Shorter follow-up time intervals and smaller dose increments can be implemented especially for the elderly, and those with other comorbidities, such as DM (**Grade A; BEL 1**).

**R39.** When maintenance rhGH doses are achieved, the following parameters may be assessed at approximately 6- to 12-month intervals: serum IGF-1, fasting glucose, hemoglobin A1c, fasting lipids, BMI, waist circumference, waist-to-hip ratio, serum-free T<sub>4</sub>, and the hypothalamic-pituitary-adrenal axis via early morning cortisol or cosyntropin stimulation test, if clinically indicated (**Grade C; BEL 2; primarily based on expert opinion of the committee**).

**R40.** When restarting rhGH therapy in transition patients, resuming rhGH at 50% of the dose used in childhood may be considered. Serum IGF-1 levels should be monitored to avoid exceeding the upper limit of the normal range (IGF-1 >2 SDS). The dose should be modified based on the clinical response, serum IGF-1 levels, side effects, and individual patient considerations (**Grade D; based on expert opinion of the committee**).

**R41.** In transition patients, annual measurements of height, weight, BMI, and waist and hip circumference are recommended, measuring bone mineral density and fasting lipids after discontinuing rhGH therapy as a baseline assessment, and subsequently every 2 to 3 years and every year, respectively (**Grade D; based on expert opinion of the committee**).

**R42.** Adults with GHD have an increased risk of cardiovascular morbidity and mortality, and currently, there are no definitive outcome data that confirm that treating this condition would mitigate this risk as long-term prospective, controlled clinical trials are still lacking. Therefore, clinicians should monitor cardiovascular parameters at 6- to 12-month intervals and include fasting lipids, systolic and diastolic blood pressure, and heart rate, while more detailed examinations such as electrocardiogram, echocardiogram, and carotid echo-Doppler examinations may be performed if clinically indicated according to local best clinical practice (**Grade C; BEL 2; based on expert opinion of the committee**).

**R43.** Adults with GHD have an increased risk of developing osteopenia and osteoporosis. Measurement of bone mineral content and bone mineral density is suggested in GH-deficient patients before starting rhGH therapy. If the initial bone dual-energy X-ray absorptiometry (DXA) scan is abnormal, clinicians should repeat bone DXA scans at 2- to 3-year inter-

vals to assess the need for additional bone-treatment modalities (**Grade C; BEL 4; upgraded by consensus based on expert opinion**).

**R44.** Clinicians should perform baseline magnetic resonance imaging (MRI) in patients with any post-surgical tumor remnant in the hypothalamic-pituitary region before initiating rhGH, and periodic MRIs during rhGH therapy (**Grade C; BEL 4; upgraded by consensus based on expert opinion**).

**R45.** Because untreated adults with GHD frequently report impaired quality of life (QoL), clinicians should consider assessing baseline QoL using specific Quality of Life in Adult Growth Hormone Deficiency Assessment (QoL-AGHDA) questionnaires before rhGH treatment is commenced, and at 12-month intervals to determine whether there is a change or sustained impact of rhGH therapy on QoL (**Grade C; BEL 4**).

**R46.** Interactions of GH with other pituitary hormone axes may affect glucocorticoid and thyroid hormone requirements; hence, these hormones should be monitored closely, especially before initiation of rhGH therapy, as introduction of these hormones or dose increments may be required while on rhGH therapy. When stable new glucocorticoid and thyroid hormone doses are established, less frequent monitoring may be undertaken, unless symptoms develop or radiotherapy is administered (**Grade B; BEL 1**).

**R47.** The optimal duration of rhGH replacement therapy remains unclear. If patients on rhGH replacement experience beneficial effects on QoL and objective improvements in biochemistry, body composition, and bone mineral density, rhGH treatment can be continued indefinitely (**Grade B; BEL 2**).

## **Q9. CAN rhGH BE USED DURING CONCEPTION AND PREGNANCY?**

**R48.** Previous studies support the use of rhGH while seeking fertility, and continuing rhGH during pregnancy does not appear to impact the outcomes of either mother or fetus. However, more data are still needed regarding the safety of rhGH. Routine use of rhGH for conception or continued use during pregnancy in women with GHD cannot be recommended at this present time (**Grade C; BEL 3**).

## **Q10. WHAT ARE THE SIDE EFFECTS OF rhGH REPLACEMENT?**

**R49.** Side effects are related mainly to fluid retention effects and are typically seen during initiation and dose escalation of rhGH, and generally respond to dose reductions or cessation of therapy. Lower doses of rhGH are recommended in obese and older patients

who are generally more susceptible to the side effects of rhGH replacement (**Grade A; BEL 1**).

**R50.** It is recommended to avoid the use of high rhGH doses to minimize the risk of side effects and aim to maintain target serum IGF-1 levels within the age-adjusted laboratory reference range (IGF-1 SDS between -2 and + 2) (**Grade A; BEL 1**).

#### **Q11. HOW SAFE IS LONG-TERM rhGH REPLACEMENT THERAPY?**

**R51.** If DM develops during rhGH therapy, or if rhGH therapy is considered in patients with concurrent DM, use of low-dose rhGH therapy, and addition and/or adjustments in antidiabetic medications are suggested. If pre-existing DM worsens while on rhGH therapy, it is reasonable to initiate or increase the doses of antidiabetic therapy or discontinue rhGH therapy and optimize treatment of DM first before considering resuming rhGH therapy in these patients (**Grade B; BEL 1**).

**R52.** Treatment with rhGH in patients with a history of active malignancy (other than basal-cell or squamous-cell skin cancers) and active proliferative or severe nonproliferative diabetic retinopathy is contraindicated (**Grade B; BEL 2**).

**R53.** Treatment with rhGH should be conducted with caution in patients with a strong family history of cancer (**Grade B; BEL 2**).

**R54.** For adults with GHD and a history of cancer who have expressed a desire to start rhGH replacement therapy, such therapy may be considered based on each individual circumstance, and low-dose rhGH therapy should only be initiated at least 5 years after cancer remission is achieved and after discussion with the patient's oncologist (**Grade D; based on expert opinion of the committee**).

**R55.** After over 20 years of adult rhGH replacement, there are no data to suggest that rhGH replacement in adults increases the risk of cancer or accelerates recurrences of tumors in the hypothalamic-pituitary region; however, for the purposes of safety surveillance, continued long-term monitoring and standard cancer screening should still be performed (**Grade B; BEL 2**).

#### **Q12. IS rhGH RECOMMENDED FOR SPORTS AND ANTI-AGING?**

**R56.** Detection of rhGH abuse poses many challenges because GH is a naturally occurring substance which has a short half-life after subcutaneous and intravenous injection, is released in a pulsatile fashion, and the levels increase after exercise. Drug testing involving urine sampling is not recommended as this method of testing has not been shown to be accurate and reli-

able, whereas repeated blood sampling over 24-hours is neither practical nor feasible in the sports setting (**Grade A; BEL 1**).

**R57.** In the U.S., off-label distribution or marketing of GH for the enhancement of athletic performance or to treat aging or aging-related conditions is illegal and punishable by imprisonment. Under no circumstances should rhGH be prescribed for sports or for "anti-aging" purposes (**Grade A; BEL 1**).

#### **Q13. WHAT ARE NEW DEVELOPMENTS IN THIS FIELD?**

**R58.** The frequency of daily injections is thought to be one of the major factors contributing to nonadherence with rhGH therapy, and weekly long-acting GH (LAGH) preparations are currently under development, which may facilitate improvement in adherence. Clinicians may follow the developments of LAGH preparations, which are currently investigational and not commercially available yet in the U.S. (**Grade C**).

#### **UPDATED EVIDENCE BASE FOR 2019**

In this update, there are 357 citations of which 51 (14%) are EL 1 (strong), 168 (47%) are EL 2 (intermediate), 61 (17%) are EL 3 (weak), and 77 (22%) are EL 4 (no clinical evidence). The evidence base presented here provides relevant information for the recommendations in the Executive Summary.

#### **Q1. WHAT IS ADULT GHD?**

Adult GHD is a well-defined clinical entity characterized by decreased lean body mass and increased fat mass, dyslipidemia, cardiac dysfunction, decreased fibrinolysis and premature atherosclerosis, decreased muscle strength and exercise capacity, decreased bone mineral density (BMD), increased insulin resistance, and impaired QoL (54). Recent studies have demonstrated increased mortality in patients with hypopituitarism (37,55-59), particularly in women and in patients diagnosed at a younger age (58,59). It is possible that GHD per se may play a role in contributing to the excess morbidity and mortality rates among patients with hypopituitarism (4,5,8), although other factors such as under- (55) or overtreatment (57,60) of glucocorticoid replacement therapy for secondary adrenal insufficiency and the underlying etiology of the hypothalamic-pituitary disease are also important contributing factors (4,5,61,62).

GHD may present as CO-GHD or AO-GHD and may occur either as IGHD or associated with MPHD. The true prevalence and incidence rate of adult GHD is difficult to estimate. A reasonable estimate may be obtained from the prevalence data for pituitary macroadenomas (63), which is approximately 1:10,000 population. Adult-onset

GHD has been estimated to affect 1 per 100,000 people annually, while its incidence rate is approximately 2 per 100,000 when CO-GHD patients are included (64), with approximately 15 to 20% of the cases being transition of CO-GHD into adulthood (65). Combining both AO-GHD and CO-GHD yields an overall prevalence of 2 to 3 per 10,000 population (66). The incidence rate appears to be higher in males in the CO-GHD group and in the AO-GHD group >45 years of age (64).

The most frequent cause of CO-GHD is idiopathic and may not be associated with other PHD. Other causes of CO-GHD include congenital causes (e.g., genetic abnormalities), brain structural defects (e.g., agenesis of corpus callosum, optic nerve hypoplasia, empty sella syndrome, encephalocele, hydrocephalus, arachnoid cyst, midline facial defects such as single central incisor, cleft lip, and cleft palate), and acquired causes (e.g., perinatal insults, brain tumors such as craniopharyngioma and germinomas, and pituitary adenomas) (Table 5) (67). By contrast, AO-GHD is most commonly acquired from hypothalamic-pituitary tumors and/or their treatment (Table 5) (67). Additionally, especially in the last decade, there has been an increasing number of studies reporting nontumoral causes of hypopituitarism associated with GHD that were previously unrecognized, such as TBI (including blast-induced TBI), subarachnoid hemorrhage (SAH), ischemic stroke, and central nervous system infections (68-73).

The primary goal of rhGH therapy in children is growth promotion to normalize final adult height (74), whereas for adult patients, the main goal of treatment is to reverse the adverse metabolic consequences of hormone deficiency and improve QoL (9). Because the primary treatment goals differ for pediatric and adult patients, the transition to final adult height represents an important juncture for re-assessment of GHD, continuation of rhGH replacement in adulthood for those patients who remain GH-deficient and planning for implementation of long-term surveillance for those patients who are GH-sufficient.

## **Q2. ARE THERE ANY DIFFERENCES BETWEEN CO-GHD VERSUS AO-GHD?**

In CO-GHD, the cause is commonly hypothalamic in origin because of impaired endogenous GHRH secretion (75), with the most frequently reported diagnosis being IGHD (76). By contrast, the majority of AO-GHD is acquired from damage to the hypothalamic-pituitary region, most often caused by tumors, or by treatment with surgery and/or radiotherapy. Due to differences in the etiology (77), phenotypic differences between adults with CO-GHD and those with AO-GHD have been described, as these differences may be related to the fact that CO-GHD occurs during development and that adults with CO-GHD may have had longer duration of being GH-deficient than AO-GHD patients.

Endogenous GH secretion declines with age (78,79), thus making it difficult to reliably differentiate between older patients with GHD and the physiologic decline of serum GH levels due to aging in normal subjects, hence the need to use GH-stimulation test/s in most patients and adopting appropriate GH cut-points. When compared with patients with AO-GHD, adults with CO-GHD tend to have lower BMI, waist-to-hip ratio, serum IGF-1 levels (77), and poorer social outcomes (80). Additionally, adults with CO-GHD due to organic hypothalamic-pituitary disease (e.g., craniopharyngioma, pituitary hypoplasia, ectopic posterior pituitary, or previous cranial irradiation) tend to have more severe long-term health consequences than those with AO-GHD, particularly with decreased muscle mass (81), BMD (82), and cardiac function (83).

## **Q3. HOW SHOULD PEDIATRIC PATIENTS WITH CO-GHD BE TRANSITIONED TO ADULT-CARE SERVICES?**

Human development significantly changes during the transition age, arbitrarily defined as starting in late puberty and ending with full adult maturation when peak bone mass is achieved (84). Teenagers undergo a period of physical growth, sexual maturation, and cognitive development, and form their own identities to achieve independence from their parents. Navigating the health care of young adults with CO-GHD becomes particularly challenging during this time, making it a high-risk period for these patients to inconsistently utilize specialized endocrine care (85). Transition patients are defined herein as adolescents (usually 15 to 18 years of age) with CO-GHD who have been treated with rhGH in childhood and have attained final adult height. In patients with persistent GHD after retesting, continuation of rhGH treatment is needed in order for these patients to obtain full somatic maturation, normalization of body composition and BMD, QoL, and lipid metabolism in adulthood (86).

Because the transition of medical care from childhood to adulthood is generally considered a vulnerable period in the life of a young person, it is very important that the transition of these patients to adult endocrine services be as seamless as possible. In fact, there is evidence that morbidity and mortality increase for young individuals following the transition from pediatric to adult services (87-89). Effective transition has been shown to improve long-term outcomes (90,91) and patient experience (92). However, despite the evidence of the risks associated with a poorly managed move to adult services and availability of potential solutions, studies continue to show that the move remains ad hoc and an unsatisfactory experience for transition patients (93).

It is a common belief by some pediatricians that transition should only begin shortly prior to transfer to adult services. Conversely, studies have shown that starting tran-



<b>Table 5</b> <b>Conditions and Treatment That Can Cause Adult Growth Hormone Deficiency (GHD), and Requirements for GH-Stimulation Testing</b>	
Testing for adult GHD is required	Testing for adult GHD is not required
<p style="text-align: center;"><i>Acquired</i></p> <ul style="list-style-type: none"> <li>Skull-base lesions</li> <li>Pituitary adenoma<sup>a</sup></li> <li>Craniopharyngioma<sup>a</sup></li> <li>Rathke's cleft cyst<sup>a</sup></li> <li>Meningioma</li> <li>Glioma/astrocytoma</li> <li>Neoplastic sellar and parasellar lesions</li> <li>Chordoma</li> <li>Hamartoma</li> <li>Lymphoma</li> <li>Metastases</li> <li>Other</li> <li>Brain injury</li> <li>Traumatic brain injury<sup>a</sup></li> <li>Sports-related head trauma<sup>a</sup></li> <li>Blast injury<sup>a</sup></li> <li>Infiltrative/granulomatous disease</li> <li>Langerhans cell histiocytosis</li> <li>Autoimmune hypophysitis (primary, secondary)</li> <li>Sarcoidosis</li> <li>Tuberculosis</li> <li>Amyloidosis</li> </ul> <p style="text-align: center;"><i>Surgery to the sella, suprasellar, and parasellar region<sup>a</sup></i></p> <p style="text-align: center;"><i>Cranial irradiation<sup>a</sup></i></p> <p style="text-align: center;"><i>Central nervous system infections</i></p> <p style="text-align: center;">Bacteria, viruses, fungi, parasites</p> <p style="text-align: center;"><i>Infarction/hemorrhage</i></p> <ul style="list-style-type: none"> <li>Apoplexy</li> <li>Sheehan's syndrome</li> <li>Subarachnoid hemorrhage</li> <li>Ischemic stroke</li> <li>Snake bite</li> </ul> <p style="text-align: center;"><i>Empty sella</i></p> <p style="text-align: center;"><i>Hydrocephalus</i></p> <p style="text-align: center;"><i>Idiopathic</i></p>	<p style="text-align: center;"><i>Pituitary hormone deficiencies ≥3 and low IGF-1</i></p> <p style="text-align: center;"><i>Congenital</i></p> <p style="text-align: center;"><i>Genetic</i></p> <ul style="list-style-type: none"> <li>Transcription factor defects (PIT-1, PROP-1, LHX3/4, HESX-1, PITX-2)</li> <li>GHRH receptor-gene defects</li> <li>GH-gene defects</li> <li>GH-receptor/post-receptor defects</li> <li>Associated with brain structural defects</li> <li>Single central incisor</li> <li>Cleft lip/palate</li> </ul> <p style="text-align: center;"><i>Acquired causes</i></p> <p style="text-align: center;">Perinatal insults</p>
<p><sup>a</sup>These items comprise the more common causes of adult GHD seen in clinical practice.</p>	

sition early at around 11 to 12 years of age leads to better knowledge and skills (94), offers the patient and caregiver more time to prepare for adult services, and allows patients to move through the process at their own individual pace. Additionally, having close collaboration, frequent communication, and common transition clinics staffed by pediatric and adult endocrinologists may be beneficial, and can take place around the time of final height and completion of puberty. The pediatrician should effectively set expectations to prepare the child and parents for the possibility that rhGH treatment might need to be resumed in adulthood. The adult endocrinologist taking over future follow-up should be aware that obtaining adult height and completing

puberty does not mean that the adolescent is fully matured in a physiologic and psychologic sense.

#### **Q4. WHAT ARE THE BENEFITS OF CONTINUING rhGH REPLACEMENT IN TRANSITION PATIENTS WITH CO-GHD?**

Low BMD, impaired bone microarchitecture and abnormal body composition tend to be more frequently observed in young adults with CO-GHD and underlying structural pituitary or brain tumors than those with idiopathic GHD (95). In these patients, the abnormal body composition may manifest as increased fat mass, decreased



lean body mass, and adverse cardiovascular risk markers, with lower high-density lipoprotein (HDL)-cholesterol and higher low-density lipoprotein (LDL)-cholesterol that is more pronounced than patients with AO-GHD (96-98). Beyond transition, a longitudinal study reported delayed timing of peak bone mass at the lumbar spine and a rapid decline in BMD over the following 2 years in adolescents with CO-GHD who discontinued rhGH treatment after final height was achieved (99), whereas in another study, a longer interval without rhGH replacement was associated with lower BMD in the femoral neck (100). Therefore, these patients are at risk of not achieving peak bone mass as a consequence of discontinuing rhGH treatment at final height.

However, studies documenting results of rhGH treatment of patients with CO-GHD have been somewhat inconsistent. Some studies have demonstrated increased BMD and improved lipid profiles after 2 years of rhGH therapy compared with untreated patients (101-103), while others have failed to show any benefit from continuation of rhGH therapy 2 years after final height is achieved (104,105). These discordant results may be explained by the fact that in the studies reporting improvement (101-103), the majority of patients had MPH (defined as  $\geq 3$  PHD other than GHD), had stopped taking rhGH therapy for 1 to 6 years, and had an average age of re-initiation of rhGH therapy of 18 to 23 years. In the 2 studies (104, 105) that did not show efficacy of rhGH therapy, the majority of patients had idiopathic IGHD, an average age of 16 years, and time without rhGH therapy of only about 1 month. Furthermore, BMD may not be a reliable method of assessment of skeletal integrity in young adults with CO-GHD because continued bone maturation in some of these patients is still ongoing in an enlarging skeleton. The positive effects of GH on cortical and trabecular microarchitecture has been demonstrated in some studies (97,106,107), and this may be more relevant in predicting future risk of fractures and prevention than actual BMD in these patients.

It is important to evaluate patients for persistence of GHD at the time of completion of longitudinal growth, as those patients who remain GH-deficient can be at risk of developing adverse metabolic outcomes upon cessation (101,108,109) that may be mitigated by resuming rhGH therapy (96,98,102,110). While the majority of patients with IGHD are not GH-deficient in adulthood (111,112), children with MPH and structural pituitary or brain tumors and/or genetic mutations are likely to remain persistently GH-deficient (67). In these patients, retesting for GHD is not required and rhGH replacement can be continued without interruption.

Current published data suggest that rhGH therapy has the greatest impact on body composition (101,103), muscle strength (113), and cardiovascular risk markers (114,115), including improvements in dyslipidemia (16), with a lesser impact on BMD (101-105), insulin sensitivity (116), and

QoL (117). Despite the lack of compelling data (118), several studies have reported that untreated GHD during the transition period can adversely impact somatic and metabolic development (100,109,119), although it remains challenging to establish whether these alterations may affect future morbidity and mortality. Larger and longer-term studies are needed to determine whether the metabolic alterations in transition GH-deficient patients persist in later adulthood, and whether continuation of rhGH replacement improves long-term overall health.

## **Q5. WHO SHOULD BE TESTED FOR ADULT GHD?**

Because the presenting symptoms and signs of adults with GHD are typically nonspecific and resemble those of the metabolic syndrome, clinicians should perform a comprehensive evaluation, including performing GH-stimulation testing in the appropriate clinical context of patients with a reasonable probability of GHD (Table 5), and with the intent to initiate rhGH replacement should the diagnosis be confirmed. The exception is that GH-stimulation testing is not required in certain patients who meet the criteria that predicts adult GHD with high specificity (120). These patients include those with organic hypothalamic-pituitary disease (e.g., suprasellar mass with previous surgery and cranial irradiation) who have MPH (defined as  $\geq 3$  pituitary hormone deficits) and low serum IGF-1 levels ( $< -2.0$  SDS) (as the probability of GHD being documented on stimulation testing is  $> 95\%$ ) (120), patients with genetic defects affecting the hypothalamic-pituitary axes, and those with hypothalamic-pituitary structural brain defects (67). In patients with  $\leq 2$  PHD, low serum IGF-1 levels ( $< -2.0$  SDS) alone cannot be used to make the diagnosis of adult GHD and clinicians should perform a GH-stimulation test to confirm the diagnosis in these patients. In contrast, after longitudinal growth is completed in transition patients with idiopathic IGHD and low-normal (between 0 to  $-2$  SDS) or low ( $< -2$  SDS) serum IGF-1 levels, GHD and deficiency of 1 or 2 additional pituitary hormones, IGHD with pituitary hypoplasia or ectopic posterior pituitary, and previous history of cranial irradiation, retesting for GHD should be performed after at least 1 month following discontinuation of rhGH therapy.

The number of GH-stimulation tests needed in transition patients with childhood IGHD or suspected hypothalamic GHD is dependent on the level of the clinician's suspicion. If the suspicion is high, such as IGHD with pituitary hypoplasia or ectopic posterior pituitary and previous cranial irradiation and a low-normal ( $< 0$  SDS) serum IGF-1 level is detected, clinicians should perform one GH-stimulation test. If the suspicion is low (e.g., in patients with no visible sellar abnormality on MRI and no other PHD) and the serum IGF-1 level is low-normal ( $< 0$  SDS), then clinicians should perform 2 different GH-stimulation

tests using appropriate peak GH cut-points. Conversely, a large number of patients with IGHD and serum IGF-1  $\geq 0$  SDS show normalization of endogenous GH secretion when retested at the time or after adult height is achieved (121,122); therefore, retesting and rhGH therapy in these patients are not required. For other transition patients with CO-GHD, it is recommended that these patients be retested to confirm the diagnosis when longitudinal growth is completed. The exception are patients with MPHD and low serum IGF-1 levels ( $< -2$  SDS) or a known hypothalamic-pituitary congenital/genetic defect, where the likelihood of GHD is high, and retesting is not required (86). Additionally, the risk for development of persistent GHD after previous childhood radiation treatment is increased with higher radiation doses and longer duration of time post-therapy (123,124). In these patients, retesting those who initially tested as GH-sufficient may be performed later in the transition period or later in adulthood. It is important to note that GHD may be associated with normal serum IGF-1 levels appropriate for age and sex in AO-GHD patients, although in these patients, serum IGF-1 levels are generally  $< 0$  SDS (125). Thus, in an appropriate clinical context with reasonable clinical suspicion, a serum IGF-1 in the bottom half of the reference range (i.e., between 0 to  $-2$  SDS) should not dissuade the clinician from considering the possibility of GHD and performing further GH-stimulation testing.

Adults with CO-GHD due to structural hypothalamic-pituitary lesions, and those with a previous history of TBI or radiation require retesting for GHD. Patients with CO-GHD who underwent GH-replacement therapy should also be retested for GHD as adults, unless the patient is known to have genetic mutations (especially in early-appearing transcription factors), or irreversible structural hypothalamic-pituitary damage. Congenital GHD is often associated with a variety of hypothalamic-stalk-pituitary anatomic abnormalities, ranging from pituitary hypoplasia to stalk agenesis and ectopically located posterior pituitary adjacent to the hypothalamus (126). For these patients, further testing for GHD after adult height is achieved may be considered if the clinical suspicion is high in these patients to assess for persistent GHD in adulthood (127,128).

Tumors in the pituitary and hypothalamic region are the most common causes of adult GHD (50) and may result in partial or complete hypopituitarism from tumor compression or following treatment with surgery and/or irradiation. The most common lesions are pituitary adenomas, craniopharyngiomas, and Rathke's cleft cysts. Other less common conditions that require testing for adult GHD include tumors in the hypothalamus (e.g., hypothalamic hamartoma) (129), infiltrative diseases of the hypothalamus and stalk (e.g., Langerhans cell histiocytosis, sarcoidosis and tuberculosis), and autoimmune hypophysitis. More recently, central nervous system infections

(130,131), ischemic stroke (68,71,72), SAH (68,69,71), meningoencephalitis (51), and hemorrhagic fever due to hantaviruses (51) are also reported as potential causes of GHD. However, as these are uncommon causes of adult GHD, confirmation of the diagnosis with GH-stimulation testing is required. Specifically, in TBI and SAH patients, GHD may be transient especially within the first year after the event (132). In these patients where there is a reasonable level of clinical suspicion, GH-stimulation testing should only be performed at least 12 months after the event (132-134).

In patients with IGHD and serum IGF-I  $\geq 0$  SDS, which accounts for the majority of individuals with childhood GHD (111,112), many will demonstrate normal GH responses when retested after final height is achieved. In these patients, retesting and rhGH therapy are not required; however, it is reasonable to continue long-term follow-up in case they develop delayed GHD. Conversely, young adults with organic GHD in childhood as a consequence of a sellar lesion, pituitary surgery, high-dose irradiation to the hypothalamic-pituitary axis, or a combination of these resulting in MPHD (135) and those with structural pituitary abnormalities (e.g., pituitary hypoplasia, pituitary stalk agenesis, and posterior pituitary ectopia) (136) often remain GH-deficient. Re-assessment for GHD is recommended to confirm the diagnosis, followed by rhGH replacement at adult doses for those patients with persistent GHD. Factors that can increase the likelihood of developing adult GHD after cranial irradiation include higher radiation doses, younger age, and a longer interval after completion of radiotherapy (137). In cases where there is no suggestive clinical history (Table 5), evaluation for adult GHD should not be performed. Recommended treatment algorithms for the transition and adult patients are shown in Figures 2 and 3, respectively.

## Q6. HOW SHOULD ONE TEST FOR ADULT GHD?

The diagnosis of adult GHD is often challenging due to lack of a single biologic endpoint, such as growth failure seen in children with the disorder. As GH levels decline with aging, it is important to differentiate between age-related physiologic decline in GH levels and pathologic GHD that usually has an identifiable cause. Additionally, GH is secreted by the pituitary gland episodically in a pulsatile pattern, and modified by age, gender, and BMI, whereas serum IGF-1 levels can be lowered by factors such as protein or calorie malnutrition, poorly controlled DM, chronic illness, renal failure, and chronic liver disease (138). Hence, random serum GH and IGF-1 levels cannot be used alone and GH-stimulation test/s may be performed to establish the diagnosis in most patients, with the exception of certain subpopulations such as those with organic hypothalamic-pituitary disease (e.g., suprasellar mass with previous surgery and cranial irradiation) who have MPHD

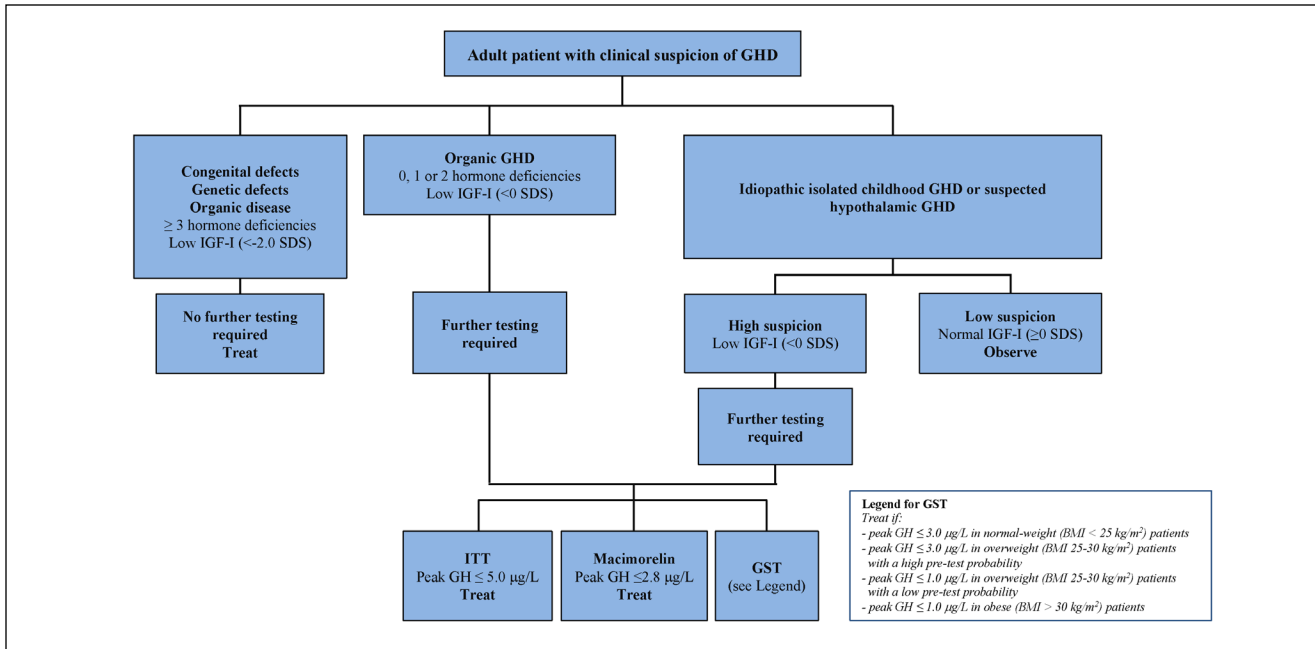


Fig. 2. Algorithm for testing transition patients with clinical suspicion of GHD.

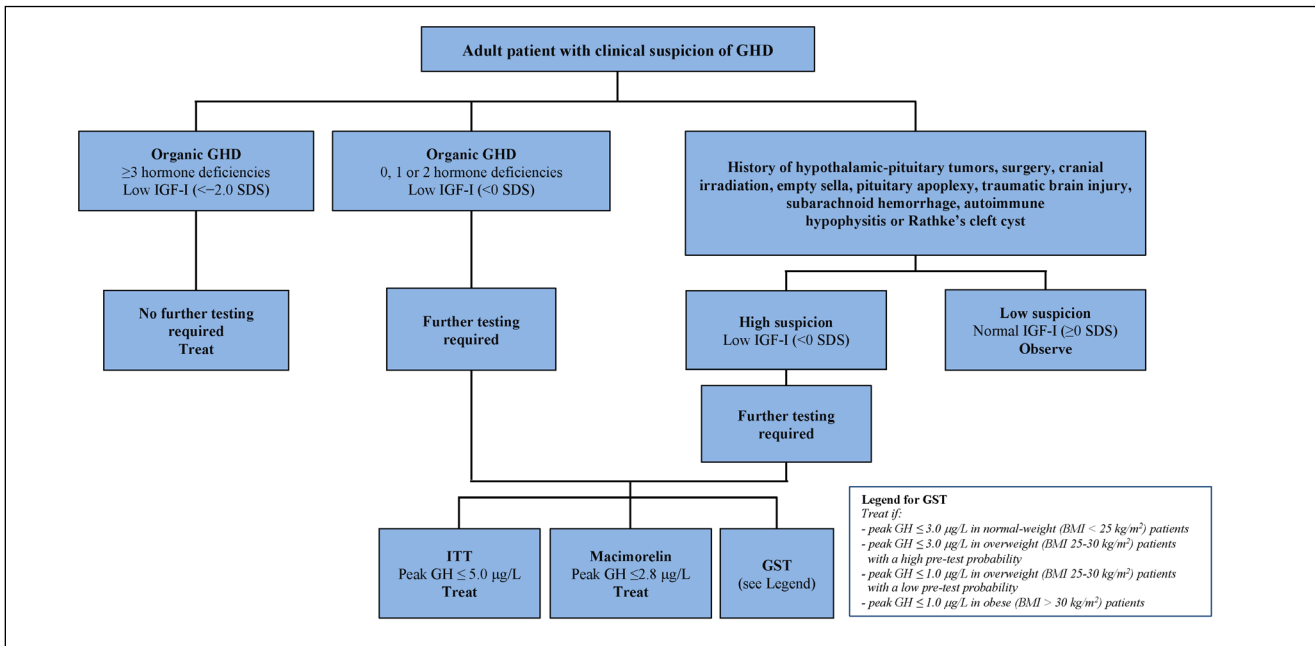


Fig. 3. Algorithm for testing adult patients with clinical suspicion of GHD.

and low serum IGF-1 levels (<-2.0 SDS) (120), patients with genetic defects affecting the hypothalamic-pituitary axes, and those with hypothalamic-pituitary structural brain defects (67).

The diagnosis of adult GHD is dependent upon the accuracy and reliability of the GH-stimulation test utilized. All GH-stimulation tests are based on the concept that a pharmacologic agent can be administered to provoke

pituitary GH secretion, with serum GH levels measured at timed serum-sampling intervals, and the peak serum GH level compared against a validated GH cut-point to interpret the test. Historically, the ITT has been widely accepted as the gold-standard GH-stimulation test, but this test is labor-intensive, contraindicated in the elderly and in adults with seizure disorders and cardio/cerebrovascular disease, can be unpleasant for the patient, and is potentially hazard-

ous. Because of these limitations associated with the ITT, this test has in recent years been used less frequently in the U.S. (139).

Finding a reliable alternative to the ITT for the diagnosis of adult GHD has been a challenge. After the removal of recombinant GHRH (injectable sermorelin) from the market in the U.S. in July, 2008, the GHRH plus ARG test could no longer be performed (140). Furthermore, ARG used alone has poor diagnostic accuracy unless a very low peak GH cut-point of 0.4  $\mu\text{g/L}$  is used (141). Therefore, based on available data (142,143), the GST was suggested as the alternative test to the ITT, replacing the GHRH plus ARG test (140). The GST has become the most commonly used diagnostic agent because of its availability, reproducibility, safety, lack of influence by gender and hypothalamic cause of GHD, and relatively few contraindications (139). The accuracy of GST is acceptable in normal-weight individuals, but because peak GH secretion decreases with increasing BMI (144,145), a lower peak GH cut-point of 1  $\mu\text{g/L}$  has been proposed for overweight/obese patients (146). The main disadvantages of the GST are its long duration (3 to 4 hours) with multiple blood draws, the need for intramuscular administration, and not infrequent gastrointestinal side effects (147). In December, 2017, the U.S. FDA approved oral macimorelin for use as a diagnostic test for adult GHD in the U.S. (148). The macimorelin test has been demonstrated to be safe, effective, highly reproducible, and has excellent tolerability, with sensitivity and specificity comparable to the ITT (149) and the GHRH plus ARG test (150). Because the macimorelin test is simple, well tolerated with minimal side effects, and of shorter duration with only 3 to 4 blood draws compared to other GH-stimulation tests, it is anticipated that its use will increase over time.

In transition patients, a feasible and validated GH-stimulation test with optimal peak GH cut-points has been less well-studied. In a systematic review by Sfeir et al (151) comparing transition patients with childhood cancer to non-childhood cancer survivors, the authors propose the use of ITT as the test of choice but not the GHRH plus ARG test given the primarily hypothalamic dysfunction of childhood cancer survivors (152). In this regard, the ITT is recommended as the test of choice even though its performance is largely based on the general population and historic experience. If the ITT is contraindicated or not feasible to perform, the GST and the macimorelin test may be considered as alternative tests, but data remain scarce regarding the peak GH cut-points for these tests in this group of patients. By contrast, ARG and L-DOPA testing have not been systematically evaluated, but because these tests have a low specificity for confirming GHD in adults (141), neither test should be used.

It is important to note that GH-stimulation test/s should only be conducted after all the other PHD have been optimally replaced with stable hormone-replacement doses because over- or under-replacement of the other endocrine axes can potentially affect the results of GH testing. Caution should also be exercised when interpreting the results of GH-stimulation tests in overweight/obese adults, especially as obesity is common in patients with tumors in the hypothalamic-pituitary region (147,154-159). Obesity is a state of functional, relative GHD, associated with decreased spontaneous secretion, pulses, and half-life of GH (78,160,161). Furthermore, nonalcoholic fatty liver disease also is increasingly observed now in overweight and obese adults with GHD (162), with diminished hepatic GH signaling (163) and lower serum IGF-1 levels (164) being associated with increasing severity of the disease. By contrast, serum IGF-1 levels are less affected by obesity per se, presumably due to increased hepatic GH sensitivity, resulting in discordance between GH and IGF-1 levels in these patients. This notion has been substantiated by a greater IGF-1 response to a single bolus of GH administration (165) and larger increments and decreased individual variability of serum IGF-1 levels to low rhGH replacement doses in obese adults with GHD (45).

Common limitations associated with currently available GH-stimulation tests include GH responses to the ITT and GST that show intra-individual variability, and a lack of normative data based on age, gender, and BMI with the ITT, GST, and macimorelin test with variable peak GH cut-points, depending on which test is used. For the ITT and GST, the peak GH cut-points have been previously accepted as 3 to 5  $\mu\text{g/L}$  and 2.5 to 3  $\mu\text{g/L}$ , respectively (34,67,153). For the macimorelin test, a peak GH cut-point of 2.8  $\mu\text{g/L}$  was suggested in 2017 by the FDA in its approval, although data from a pivotal Phase-3 trial indicated that higher sensitivity can be achieved while maintaining high specificity using a higher GH cut-point of 5.1  $\mu\text{g/L}$  (149), suggesting that this higher GH cut-point could accurately capture all the GH-deficient patients and did not misclassify those who were GH-sufficient. Another limitation associated with currently available GH-stimulation tests include the paucity of data for specific populations of adult GHD, such as patients with TBI, uncontrolled DM, SAH, and transition patients. An ideal GH-stimulation test should possess several desired characteristics that include the ability to reliably distinguish patients with GHD patients from GH-sufficient individuals, safe and easy accessibility of the test agent, high test reproducibility, and little to minimal side effects. From a practical standpoint, it would be advantageous if the test is inexpensive, simple and quick to perform. The different test characteristics of currently available GH-stimulation tests in the U.S. are summarized in Table 6.



**Table 6**  
**Different Characteristics of Available GH-Stimulation Tests**

Test	Accurate?	Safe?	Tolerability?	Simple?	Speedy?	Available?	Cost?
ITT	“Gold standard”	No (in some patients)	No (in some patients)	No	No	Yes	\$
GST	Yes <sup>a</sup>	Yes	No (in some patients)	Yes	No	Yes	\$
Macimorelin	Yes	Yes	Yes	Yes	Yes	Yes	\$\$\$

Abbreviations: BMI = body mass index; GH = growth hormone; GST = glucagon stimulation test; ITT = insulin tolerance test.  
<sup>a</sup>If appropriate BMI-dependent GH cut-points are utilized.

### Q6.1. GH–stimulation tests currently available in the U.S.

#### *Insulin Tolerance Test*

The ITT has historically been accepted as the “gold standard” test for the assessment of adult GHD, with a GH cut-point of 3 to 5  $\mu\text{g/L}$  when adequate hypoglycemia (blood glucose  $<40$  mg/dL) is achieved. This GH cut-point was initially proposed by Hoffman et al (166) in 1994 based on GH responses to insulin-induced hypoglycemia, mean 24-hour serum GH levels derived from 20-minute sampling, and serum IGF-1 and insulin-like growth factor-binding protein (IGFBP)-3 levels in 23 patients considered GH-deficient due to organic pituitary disease, and in 35 sex-matched normal subjects of similar age and BMI. The ranges of stimulated peak GH responses separated GH-deficient (0.2 to 3.1  $\mu\text{g/L}$ ) from GH-sufficient (5.3 to 42.5 ng/mL) patients. However, there was overlap in mean serum 24-hour GH, IGF-1, and IGFBP-3 levels demonstrating the challenge in utilizing these biochemical tests alone to reliably determine GH reserve.

Disadvantages of the ITT are that it requires close medical supervision by a physician, is unpleasant for patients as it can cause severe hypoglycemia, and has important potential adverse effects (e.g., seizures and altered consciousness resulting from neuroglycopenia). This test is contraindicated in the elderly and in patients with a history of cardiovascular and cerebrovascular disease and seizures. Furthermore, inducing adequate hypoglycemia in normoglycemic and/or hyperglycemic obese patients with insulin resistance (167) may be challenging, necessitating the use of higher insulin doses (0.15 to 0.2 IU/kg), thus increasing the risk of delayed hypoglycemia after test completion. Although the ITT demonstrates good sensitivity, its lack of reproducibility on repeat testing is another limitation. Differences in peak GH responses have been demonstrated in healthy subjects undergoing ITT at varying times (168) and in women at different times of their menstrual cycle (169).

#### *Glucagon-Stimulation Test*

Glucagon is relatively more potent than ARG or clonidine in stimulating GH secretion (170,171) and has been assessed in elderly subjects (172) and against the ITT in evaluating GH reserve in patients following pituitary

surgery (173). However, the mechanisms of the GH–stimulatory effect of glucagon remain unclear.

Gomez et al (143) and Conceicao et al (142) compared the diagnostic characteristics of GST to ITT and included a control group matched for age and sex in both studies, and for BMI in one study (143). Both studies demonstrated that a GH cut-point of 3  $\mu\text{g/L}$  provided optimal sensitivity and specificity (142,143). Gomez et al (143) also found an inverse correlation between age ( $R = -0.389$ ,  $P < .01$ ) and BMI ( $R = -0.329$ ,  $P < .05$ ) with peak GH levels in healthy controls. However, it is important to note that this study was conducted in a European cohort, where obesity is less prevalent than the U.S. population (174). By contrast, Conceicao et al (142) demonstrated that peak GH levels were not affected by age in either the control or patient group, and there were no sex differences. In another study, Berg et al (173) demonstrated a lower peak GH cut-point of 2.5  $\mu\text{g/L}$  with 95% sensitivity and 79% specificity. This study reported lower peak GH levels with GST compared to ITT (5.1 versus 6.7  $\mu\text{g/L}$ ,  $P < .01$ ) and a positive correlation between peak GH levels during ITT and GST ( $R = 0.88$ ,  $P < .0001$ ), but no correlation between BMI or age to peak GH responses (175,176). However, these (142,143,173) and other studies (170,171,177,178) did not specifically evaluate patients with hyperglycemia and glucose intolerance. Hence, the diagnostic accuracy of the GST in testing for GHD in patients with glucose intolerance remains unclear.

Advantages of the GST are its reproducibility, safety, and lack of influence by sex and hypothalamic origin of the GHD (140), whereas disadvantages include the long test duration (3 to 4 hours) with multiple blood draws, and the fact that an intramuscular injection is required. Commonly reported side effects include nausea, vomiting, and headaches ranging from  $<10\%$  (173) to 34% (175), and mainly occur between 60 to 210 minutes; side effects tend to resolve by 240 minutes into the test (147). The side effects of the GST have been reported to be more pronounced in elderly subjects with underlying cardiovascular and neurologic comorbidities, where symptomatic hypotension, hypoglycemia, and seizures may be potentiated (179).

Previous studies have examined the diagnostic utility of the GST for adult GHD, but BMI was not taken into consideration (142,173) or included only controls with normal BMIs (170,171). Several retrospective studies have



questioned the diagnostic accuracy of the GST when the GH cut-point of 3 µg/L is used in obese/overweight adults (147,155,159) and in those with glucose intolerance (147, 159). In a prospective study performed by Hamrahian et al (157), improved diagnostic accuracy was demonstrated when a lower GH cut-point was utilized. Yuen et al (147) evaluated GSTs performed in 515 patients, and found that BMI, and fasting, peak, and nadir glucose levels inversely correlated with peak GH levels. Dichtel et al (155) evaluated 3 groups of overweight/obese men: controls who were younger than the patients, patients with 3 to 4 pituitary hormone deficits, and patients with 1 to 2 pituitary hormone deficits. Using receiver operating characteristic (ROC) analysis, a GH cut-point of 0.94 µg/L provided optimal sensitivity (90%) and specificity (94%), whereas BMI and the amount of visceral adipose tissue inversely correlated with peak GH levels in controls. Almost half of the healthy overweight/obese individuals (45%) failed the GST using the 3 µg/L GH cut-point. Diri et al (156) evaluated 216 patients with pituitary disease and 26 healthy controls and compared the GST to the ITT. These investigators used a GH cut-point of 3.0 µg/L for the ITT and 2 GH cut-points of 3.0 µg/L and 1.07 µg/L for the GST, yielding the diagnosis of adult GHD in 86.1%, 74.5%, and 54.2% of patients, respectively. In addition, patient age, BMI, and number of pituitary hormone deficits correlated with IGF-1 and peak GH levels. Twelve out of 26 (46.2%) healthy subjects failed the GST using a GH cut-point of 3.0 mg/L, but none were misclassified when the cut-point was lowered to 1.07 µg/L. Wilson et al (159) studied 42 patients with a high pretest probability of adult GHD. After excluding 10 patients with severe GHD based on peak GH levels  $\leq 0.1$  mg/L, these investigators found that body weight negatively correlated with GH area under the curve ( $R = -0.45$ ;  $P = .01$ ) and peak GH response ( $R = -0.42$ ;  $P = .02$ ) and positively correlated with nadir blood-glucose levels ( $R = 0.48$ ;  $P < .01$ ). By contrast, nadir blood-glucose levels during GSTs inversely correlated with GH area under the curve ( $r = -0.38$ ;  $P = .03$ ) and peak GH ( $r = -0.37$ ;  $P = .04$ ), implying that patients with higher nadir blood-glucose levels tended to have a lesser GH response to glucagon stimulation. Finally, Hamrahian et al (157) compared the fixed-dose GST (FD-GST: 1 mg or 1.5 mg in patients  $>90$  kg body weight) and weight-based GST (WB-GST: 0.03 mg/kg) with the ITT using a GH cut-point of 3.0 µg/L. Patients with hypothalamic-pituitary disease and 1 to 2 ( $n = 14$ ) or  $\geq 3$  ( $n = 14$ ) PHD, and 14 control subjects matched for age, sex, estrogen status, and BMI underwent the ITT, FD-GST, and WB-GST in random order. Using ROC analysis, the optimal GH cut-point was 1.0 (92% sensitivity, 100% specificity) for FD-GST and 2.0 µg/L (96% sensitivity and 100% specificity) for WB-GST.

It remains unclear whether hyperglycemia influences peak GH responses to glucagon stimulation independent of central adiposity, and whether different GH cut-points should be used for patients with underlying impaired

glucose tolerance or DM when being tested by the GST. Furthermore, no peak GH responses have been studied using the GST in normal controls  $>70$  years of age, and none of the previous studies included patients with uncontrolled DM. Studies by Yuen et al (147) and Wilson et al (159) have shown that higher blood-glucose levels during the GST were associated with lower peak GH responses; hence, caution is recommended when interpreting abnormal GST results in patients with glucose intolerance. In light of these findings (147,155-157,159), we recommend utilizing BMI-appropriate peak GH cut-points for the GST to diagnose adult GHD to reduce the possibility of misclassifying patients with adequate endogenous GH secretion as GH-deficient. For normal-weight (BMI  $<25$  kg/m<sup>2</sup>) and overweight (BMI 25 to 30 kg/m<sup>2</sup>) patients with a high pretest probability, we recommend using the GH cut-point of 3 µg/L, whereas for obese (BMI  $>30$  kg/m<sup>2</sup>) and overweight (BMI 25 to 30 kg/m<sup>2</sup>) patients with a low pretest probability, we recommend using the lower GH cut-point of 1 µg/L.

#### **Macimorelin Test**

Macimorelin (formerly known as AEZS-130, ARD-07, and EP-01572) is an orally active ghrelin-mimetic that binds to the ghrelin GHS-R1a receptor with similar affinity to ghrelin. It is a pseudotripeptide with increased stability and oral bioavailability compared with other GH secretagogues, such as GHRP-6. It is readily absorbed in the gastrointestinal tract and effectively stimulates endogenous GH secretion in healthy volunteers with good tolerability (180).

An open-label, crossover, multicenter trial tested the diagnostic accuracy of a single oral dose of macimorelin (0.5 mg/kg) compared to GHRH plus ARG in adults with GHD and healthy matched controls (150). Peak GH levels were  $2.36 \pm 5.69$  and  $17.71 \pm 19.11$  µg/L in adults with GHD and healthy controls, respectively, with an optimal GH cut-point ranging between 2.7 and 5.2 µg/L (150). Macimorelin showed good discrimination comparable to GHRH plus ARG, with peak GH levels that were inversely associated with BMI in controls. In another open-label, randomized, 2-way crossover study, oral macimorelin was compared to the ITT (149). Using GH cut-point levels of 2.8 µg/L for macimorelin and 5.1 µg/L for ITT, negative agreement was 95.4% (95% confidence interval [CI], 87 to 99%), positive agreement was 74.3% (95% CI, 63 to 84%), sensitivity was 87%, and specificity was 96%. Macimorelin was found to be well-tolerated, reproducible, and safe. Based on these data (149,150), the U.S. FDA approved macimorelin for use as a diagnostic test for adult GHD in December, 2017, and selected the GH cut-point of 2.8 µg/L to differentiate patients with normal GH secretion from those with GHD. However, when the GH cut-point was increased to 5.1 µg/L and used for both tests, negative agreement remained unchanged at 94% (95% CI, 85 to 98%), positive agreement was higher at 82% (95% CI, 72 to

90%), and sensitivity was increased to 92% while specificity remained unchanged at 96% (149). Because measured serum GH levels are dependent on the GH assays used, it is important to note that the 5.1  $\mu\text{g/L}$  is identical to the cut-point accepted for the ITT (141) and may be considered in patients with a high pre-test probability to allow clinicians using a different GH assay to apply a cut-point related to the assay used to evaluate ITT results in their local laboratory.

Advantages of the macimorelin test is that there is no need for parenteral administration compared to the ITT, GHRH plus ARG, or GST, and no concern for hypoglycemia. In addition, the duration of the test is only 90 minutes, with only 4 sample collections required, in contrast with more sample collections over 2 hours for the ITT and 3 to 4 hours for the GST. One of the limiting factors of this test is the cost of the drug (one 60 mg macimorelin packet costs approximately \$4,500) (181), which is relatively more expensive than insulin and glucagon. Mild dysgeusia was the most commonly reported side effect, which did not require any intervention and resolved spontaneously (149). Importantly, there are potential drugs that may interact with macimorelin and cause prolongation of the QT interval or reduce plasma macimorelin concentrations leading to false-positive test results (149). Hence, careful assessment of the patient's concurrent medications is recommended as well as discontinuation of strong CYP3A4 inducers, provided this is considered safe by the prescribing physician and with sufficient washout time prior to testing.

Following its approval by the FDA in December, 2017, and because macimorelin is a shorter and simpler alternative to other agents, this test is expected to be utilized more frequently over time, particularly if the cost of macimorelin becomes more affordable. However, further studies with larger number of patients including children, adolescents, elderly, and those with obesity, DM, TBI, SAH, and renal or hepatic dysfunction will be needed to determine the sensitivity and specificity of macimorelin in these subpopulations. Furthermore, in patients with hypothalamic defects, it is not clear whether the macimorelin test may yield false-positive results. Future studies are needed to improve the palatability of this drug and to help outline any potential safety issues associated with this test (i.e., concomitant use with drugs that induces QT prolongation). Hence, with this notion, the GST and the macimorelin test could be considered as alternative tests if the ITT is contraindicated or not feasible to be conducted in some patients.

#### **Q7. WHY ARE STANDARDIZED GH AND IGF-1 ASSAYS IMPORTANT IN THE MANAGEMENT OF ADULT GHD?**

Accurate measurement of serum GH and IGF-1 levels is critical for making the diagnosis of adult GHD. Specific GH cut-point levels on GH-stimulation tests must be

interpreted in the context of the analytical method used. Circulating GH is present in several different isoforms and isomers, including the most common variant of 22 kd, and other smaller molecules, such as the 20 kd GH variant (182). Monoclonal antibodies that bind to a specific molecular form of GH are used to limit detection to the 22 kd GH, without detecting other GH isoforms. Other molecules that are similar to GH (e.g., placental GH) could potentially cross-react and affect the measurement of GH levels. GH-binding protein, to which ~50% of circulating GH is bound, can also cause interference in GH assays.

Substantial heterogeneity exists among currently utilized assays due to different standard preparations for calibration of GH immunoassays and lack of harmonization between various GH assays. This makes it difficult to directly compare diagnostic cut-points across different published studies. Another source of confusion when interpreting data from GH-stimulation tests has been that some laboratories report GH levels in mU/L, whereas others have used  $\mu\text{g/L}$  (183). Differences in IGF-1 assay performance should also be considered when evaluating for GHD and while monitoring GH replacement. A robust reference population is necessary, with details provided by the laboratory. This is especially true for IGF-1, since there are physiologic changes based on gender, age, and probably several other factors that have not been well established. Thus, it is recommended that all assay manufacturers adopt the standards provided by the National Institute for Biological Standards and Control and report their methodology to clinicians by indicating the validation of their assay, which should include specification of the GH isoforms detected (20 kd GH, 22 kd GH, and other isoforms), the analyte being measured, the specificities of the antibodies used, and the presence or absence of GH-binding protein interference. The adoption of this recommendation might lead to improvement in the accuracy of diagnosis and follow-up of pathologic conditions, and facilitate the comparison of results from different assays.

To demonstrate the potential discrepancies among GH and IGF-1 assays, samples of identical concentrations were sent to laboratories in the United Kingdom as part of the United Kingdom National External Quality Assessment Service (184). These identical samples were analyzed by 104 centers for the GH sample and 23 centers for the IGF-1 sample, utilizing 14 distinct GH assay techniques and 6 IGF-1 assay techniques. Serum GH and IGF-1 levels demonstrated a 2.5-fold difference between the lowest and highest results from the various assays, with differences that classified the same patient as having the disease in one laboratory and normal in another laboratory. These data emphasize the importance of using the same GH and IGF-1 assay from the same laboratory for a given patient during evaluation, and if possible, using the same IGF-1 assay from the same laboratory throughout follow-up.

**Q7.1. What are some aspects of hormone measurements that help standardize laboratory results?**

Over the past decade, there have been consensus statements addressing the measurement of serum GH and IGF-1 levels, and there have been calls for harmonization and standardization of techniques (185). Laboratory results can be improved with the use of a single universally accepted standard preparation for GH and for IGF-1. International standards for GH and IGF-1 are both available. The second international standard for somatropin, which is a recombinant DNA-derived human GH standard 98/574 has been assigned units of 1.95 mg per ampule and has a conversion of 1 mg to 3 IU, with recommended reporting in mass units (185). IGF-1 international standard 02/254 is the most current World Health Organization–approved reference standard for IGF-1 and has been analyzed in several laboratories for purity, activity, and stability (185).

**Q7.2. Are there other ways to improve GH and IGF-1 assay reliability?**

Implementing certain measures may improve the reliability of serum GH and IGF-1 measurements. In addition to using the World Health Organization reference standard 02/254 for IGF-1, standard reference samples should be available for quality control. Methods that either eliminate or minimize binding-protein interference should be implemented, validated, and communicated as part of the results for each assay. Methods employed to reduce or eliminate GH-binding protein and IGFBP interference should demonstrate efficacy. Conditions such as DM, malnutrition, chronic liver disease, and renal diseases that can interfere with serum IGF-1 measurement (138) should be studied further, and reliable sera from healthy subjects and from such patients should be employed for validation of assays. Normative IGF-1 assay data should include a sufficient random sample of individuals from a wide range of ages, with those individuals taking medication and with conditions known to affect the GH-IGF-1 axis excluded. Results should be reported in both mass units and as an SDS score (also known as a Z-score) to allow for inter-assay comparison. The same GH assay should be used when comparing the results of different GH-stimulation tests in the same patient.

**Q8. HOW SHOULD INITIATION AND MONITORING OF rhGH REPLACEMENT BE UNDERTAKEN?**

In the U.S., rhGH (somatropin marketed under various trade names) is approved by the FDA for adult GHD. As somatropin is synthetic human GH, there is no evidence that one commercial product is different or more advantageous than another, apart from differences in pen devices,

electronic auto-injector devices that are user-friendly, dose per mg adjustments, and whether the product requires refrigeration. Therefore, one rhGH commercial product is not recommended over another because there are no prospective head-to-head trials comparing the clinical efficacy of one commercial product with another.

Serum IGF-1 levels remain the most widely used biomarker for rhGH dose adjustments even though these levels correlate weakly with clinical endpoints in rhGH treatment (186). In a randomized open-label, clinical study, van Bunderen et al (46) demonstrated that in adults treated with rhGH replacement to reach a high-normal IGF-1 target level, waist circumference decreased, and QoL improved compared to those with a low-normal IGF-1 target level, but higher serum IGF-1 levels were associated with more myalgia, and lower serum IGF-1 levels with more general fatigue. More recent data by the same group of investigators (47) showed that female patients may have a narrower therapeutic dose window; a high-normal IGF-1 target level was associated with impaired prefrontal cognitive functioning, whereas a low-normal target IGF-1 level was observed in patients with decreased vigor.

It is recommended that patients be started on a low initial rhGH dose, independent of body weight but guided by age, gender, and concomitant medications. The exceptions are young women, especially those on oral estrogen replacement or oral contraceptives, and transition patients, who may require higher initial and final doses (187-189). On balance, it is reasonable to start with rhGH doses of 0.3 to 0.4 mg/day in patients <30 years old, 0.2 to 0.3 mg/day in patients between 30 to 60 years old and lower doses of 0.1 to 0.2 mg/day in older (>60 years old) patients, obese patients, patients with DM, and patients susceptible to glucose intolerance with gradual dose up-titration to minimize the risk of rhGH-induced glucose tolerance (Table 7). After starting rhGH therapy, it is recommended to follow up patients at 1- to 2-month intervals initially and to consider increasing rhGH doses in increments of 0.1 to 0.2 mg/day. Data are scarce regarding the ideal target serum IGF-1 level.

As a general rule, it is recommended to titrate the rhGH dose to reach serum IGF-1 levels within the age-adjusted reference range provided by the laboratory utilized (IGF-1 SDS between -2 and +2). However, this decision should take into consideration the patient's pretreatment IGF-1 SDS and the circumstances and tolerability of each individual patient. Because some patients may only tolerate lower rhGH doses frequently limited by side effects, whereas others may tolerate and require higher rhGH doses to achieve the desired clinical effects, the goals of treatment for each individual patient should be the clinical response, avoidance of side effects, and targeting serum IGF-1 levels to fall within the age-adjusted reference range (IGF-1 SDS between -2 and +2). Once maintenance doses are achieved, follow-up can be implemented at 6- to 12-month

**Table 7**  
**American Association of Clinical Endocrinologists Recommendations for Recombinant Human Growth Hormone (rhGH) Replacement Therapy in Adults With Growth Hormone Deficiency (GHD)**

*Starting doses:*

Individual patient characteristics (e.g., fitness, comorbidities and overall health risk) should be taken into consideration when deciding on starting doses. Below are suggested starting doses:

- Age <30 years: 0.4-0.5 mg/day (may be higher for patients transitioning from pediatric treatment)
- Age 30-60 years: 0.2-0.3 mg/day
- Age >60 years: 0.1-0.2 mg/day

*In transition patients, we recommend to resume rhGH at 50% of the dose used in childhood.*

*In patients with concurrent DM, obesity, older age, and previous gestational DM, we recommend starting at lower rhGH doses (e.g., 0.1-0.2 mg/day).*

*Dose titration:* At 1- to 2-month intervals, increase dose in increments of 0.1-0.2 mg/day based on clinical response, serum IGF-1 levels, side effects, and individual considerations such as glucose intolerance (where lower doses may be safer) or use of oral estrogen (where higher doses may be needed to achieve target IGF-1 SDS). Longer time intervals and smaller dose increments may be necessary in older patients and those with other comorbidities such as DM.

*Goals:* Aim to increase serum IGF-1 levels to reach between age-adjusted IGF-1 SDS  $-2$  and  $+2$ , unless side effects occur. Consider a trial of higher rhGH doses, aiming for serum IGF-1 levels to determine whether this provides further benefit as long as the IGF-1 SDS does not exceed  $+2$ , as quoted by the laboratory utilized, and the patient does not experience side effects.

*Monitoring:* Approximately 6- to 12-month intervals once maintenance doses are achieved. Monitoring should include clinical evaluation and assessment of side effects, serum IGF-1, fasting glucose, hemoglobin A1c, fasting lipids, BMI, waist circumference, waist-to-hip ratio, serum-free  $T_4$ , and the hypothalamic-pituitary-adrenal axis via early morning cortisol or cosyntropin-stimulation test (in patients not on glucocorticoid replacement), if clinically indicated, at approximately 6- to 12-month intervals, and QoL measurements annually. If the initial bone DXA scan is abnormal, repeat evaluations at 2- to 3-year intervals are recommended. If a pituitary lesion is present, baseline and periodic MRIs should be undertaken according to local best clinical practice. Patients on concurrent levothyroxine and glucocorticoid hormone replacement may need dose increments after starting GH replacement therapy and patients not already on levothyroxine or glucocorticoid replacement should be monitored for the possibility of deficiencies, with replacement given if needed.

*Special situations:* It is important to retest patients transitioning from pediatric to adult care, especially those who had IGHD, after at least 1 month following discontinuation of rhGH therapy, and consideration needs to be given to minimize lengthy interruptions in rhGH therapy for those with confirmed GHD.

*Length of rhGH therapy:* The appropriate length of rhGH therapy is unclear. If benefits are achieved, treatment can be continued indefinitely. But, if no apparent or objective benefits of treatment are achieved after at least 12-18 months, discontinuing rhGH therapy may be considered. If patients decide to discontinue rhGH replacement therapy, a 6-month follow-up appointment is recommended, because some patients may wish to resume therapy, noting in retrospect that they did feel better on treatment.

Abbreviations: BMI = body mass index; DM = diabetes mellitus; DXA = dual-energy X-ray absorptiometry; GH = growth hormone; IGF-1 = insulin-like growth factor-1; IGHD = isolated growth hormone deficiency; MRI = magnetic resonance imaging; QoL = quality of life; SDS = standard deviation score;  $T_4$  = thyroxine.

intervals. Shorter follow-up time intervals and smaller dose increments may be needed for elderly patients and those with other comorbidities such as DM to assess tolerability and side effects of therapy. Table 8 summarizes the various factors to consider in rhGH dose selection in adults with GHD.

In transition patients, resuming rhGH doses at 50% of the dose last used in childhood is suggested, as these patients tend to be more tolerant of higher doses. The dose of rhGH should be gradually adjusted; it is suggested to titrate the dose to achieve the normal range of age-adjust-

ed IGF-1 SDS and to avoid exceeding the upper limit of the normal range (IGF-1  $>2$  SDS), with dose adjustments based on clinical response and avoidance of any adverse effects (Table 8). Height, weight, BMI, and waist and hip circumference can be measured annually, whereas BMD and fasting lipids can be measured after discontinuing rhGH therapy as a baseline assessment, and subsequently every 2 to 3 years and every year, respectively.

Subcutaneous injections are administered in the evening to mimic physiologic endogenous GH secretion (190). The high degree of interindividual variability in



<b>Table 8</b> <b>Factors That May Affect Changes in rhGH Dosing</b>	
<b>Increase rhGH dose</b>	<b>Decrease rhGH dose</b>
<ul style="list-style-type: none"> <li>• Young patients regardless of onset type</li> <li>• Low serum IGF-1 levels</li> <li>• Addition of oral estrogen</li> <li>• Change from transdermal to oral estrogen</li> </ul>	<ul style="list-style-type: none"> <li>• Elderly patients</li> <li>• High serum IGF-1 levels</li> <li>• Discontinuation of oral estrogen</li> <li>• Change from oral to transdermal estrogen</li> <li>• Worsening glucose tolerance</li> <li>• Side effects due to fluid retention</li> </ul>
Abbreviations: IGF-1 = insulin-like growth factor-1; rhGH = recombinant human growth hormone.	

both subcutaneous rhGH absorption and GH sensitivity (191) makes an individualized, stepwise upward titration method preferable to standard weight-based dosing strategies. Women using oral estrogen as replacement therapy or for contraceptive purposes are more GH-resistant than men (192,193) because estrogen attenuates GH action on the liver, the principal site of IGF-1 synthesis, resulting in lower IGF-1 generation (194,195). Women require more exogenous GH than men to achieve comparable IGF-1 SDS, and even with higher doses, the effects of rhGH on body composition in women may be blunted (196). Switching women to transdermal estrogen patches may allow lower rhGH doses to be used for equivalent IGF-1 responses (187), presumably by lowering the estrogen exposure to the liver. Given the expense of rhGH therapy, using estrogen patches instead of tablets to facilitate the use of lower GH doses may be a cost-effective measure.

Monitoring other pituitary hormone axes also should be undertaken closely after commencement of rhGH replacement therapy, as there may be interactions with other concurrent hormone replacements (197). Replacement of rhGH has been reported to decrease serum-free thyroxine (T<sub>4</sub>) and increase thyronine (T<sub>3</sub>) levels by increasing the extrathyroidal conversion of T<sub>4</sub> to T<sub>3</sub> without altering thyroid-stimulating hormone levels in some studies (198-201). In addition, serum cortisol levels may decline because rhGH therapy can inhibit the enzyme 11  $\beta$ -hydroxysteroid dehydrogenase type 1, resulting in a shift in cortisol metabolism favoring cortisone production (202). Although the changes are generally relatively small and do not produce significant clinical effects in most patients, occasionally these effects of rhGH on free T<sub>4</sub> and cortisol may unmask clinical central hypothyroidism (203) and hypoadrenalism (202). Hence, regular monitoring of serum-free T<sub>4</sub> levels during rhGH treatment is recommended in patients with central hypothyroidism, and in patients already on levothyroxine replacement, these doses should be increased as necessary. By contrast, in GH-deficient patients with low-normal serum-free T<sub>4</sub> levels, levothyroxine replacement may be considered before starting rhGH therapy. Similarly, the hypothalamic-pituitary-adrenal axis should be assessed before and during rhGH therapy (204). Any clinical deterioration after starting rhGH may be related to unmask-

ing of central hypoadrenalism, either newly developed in those without a prior diagnosis of central hypoadrenalism or insufficient dosing of glucocorticoids in patients already taking replacement. Hence, testing for central hypoadrenalism is recommended in patients not already on glucocorticoid replacement who develop symptoms of adrenal insufficiency on initiation of rhGH or after a dose increase. In patients already on glucocorticoid replacement, small increases of the glucocorticoid dose may be helpful in determining whether insufficient replacement was the underlying cause of the symptoms. When stable new glucocorticoid and thyroid hormone doses are established, less frequent monitoring may be undertaken, unless symptoms develop or radiotherapy is administered.

Once stable rhGH doses are maintained, clinicians should monitor the following parameters at approximately 6- to 12-month intervals: serum IGF-1, fasting glucose, hemoglobin A1c, fasting lipids, BMI, waist circumference, waist-to-hip ratio, serum-free T<sub>4</sub>, and the hypothalamic-pituitary-adrenal axis via early morning cortisol or cosyntropin-stimulation test (in patients not on glucocorticoid replacement), if clinically indicated. Additionally, evaluation of overall clinical status including assessment of QoL using the specific QoL-AGHDA questionnaire (205,206) at 12-month intervals is suggested. Because adults with GHD have an increased risk of cardiovascular morbidity and mortality, based on expert opinion of the committee, cardiovascular parameters to consider monitoring during follow-up include systolic and diastolic blood pressure, and heart rate, while more detailed examinations such as electrocardiogram, echocardiogram, and carotid echo-Doppler examinations may be performed if clinically indicated according to local best clinical practice. As noted above, a low threshold for assessing the hypothalamic-pituitary-adrenal axis via early morning cortisol or cosyntropin-stimulation test (in patients not already taking glucocorticoid replacement) is suggested whenever patients experience symptoms suggestive of adrenal insufficiency, particularly after a dose increase of rhGH is made. Measurements of bone mineral content and BMD at baseline before starting rhGH therapy should be undertaken, and if the initial bone DXA scan is abnormal, bone DXA scans should be repeated at 2- to 3-year intervals to assess



the need for additional bone-treatment modalities. In cases where the etiology of GHD was a tumor in the hypothalamic-pituitary region, baseline and periodic MRI scans should be undertaken before and during rhGH therapy to monitor the size of the pituitary lesion or any changes in post-surgical residual tumor. The parameters to monitor in adults with GHD while on GH replacement are summarized in Table 9.

An important question that is frequently debated is whether rhGH administration should be continued throughout life. Other pituitary replacement hormones are continued indefinitely, with the exception of estrogen. If patients taking rhGH replacement report significant QoL benefits and/or there are objective improvements, such as in cardiovascular risk markers, BMD, body composition, or physical activity tolerance, then rhGH treatment can be continued indefinitely (10,207-210). If there are neither subjective nor objective benefits of treatment after at least 12 to 18 months of treatment, the option of discontinuing rhGH treatment can be discussed with the patient. If treatment is discontinued, a 6-month follow-up appointment with the patient is recommended because some patients may reconsider resuming rhGH replacement therapy, noting in retrospect that their QoL was better while on treatment.

#### Q9. CAN rhGH BE USED DURING CONCEPTION AND PREGNANCY?

Growth hormone and the gonadotropic axis are inter-related throughout life, starting with the regulation of onset of puberty (211). Mechanistic studies have shown that GH and IGF-1 can stimulate the hypothalamic-pituitary-gonadal axis at all levels (212) by influencing gonadotropin release, estradiol production by granulosa cells, oocyte maturation, fertility and lactation, and

enhanced ovarian response to gonadotropins (212-215). Furthermore, dynamic changes of other hormones occur during pregnancy, paralleled by the development of the placenta, which secretes placental GH. During pregnancy, circulating placental GH levels rise, peaking at 36 weeks to levels comparable to those seen in acromegaly. This is accompanied by a sharp decline in pituitary GH levels that become undetectable by the 24th week of gestation (216). Therefore, the true benefit of rhGH replacement in women with GHD at the time of pregnancy remains unclear.

Because GH stimulates the hypothalamic-pituitary-gonadal axis at all levels, there is evidence that GHD may negatively affect the maturation of reproductive organs, delay the onset of puberty, and decrease ovarian function and fertility. Female patients with childhood-onset hypopituitarism have lower fertility rates (217) and poorer pregnancy outcomes (218). Although rhGH use during conception and pregnancy is not approved by the FDA, there have been questions about rhGH use for achieving fertility and whether patients taking rhGH replacement have satisfactory pregnancy outcomes. When rhGH was administered as an adjuvant treatment in in vitro fertilization/intracytoplasmic sperm injection cycles for poor responders, Bassiouny et al (219) reported no identifiable impact on pregnancy outcomes. However, its place in routine in vitro fertilization and ovulation induction treatment cycles is still debatable. Part of the difficulty in clarifying the place (or lack of) for rhGH in the treatment of female infertility is that the drug is expensive, it is unclear what the appropriate dose to study is, when in (or before) a cycle it should be employed, or even in which subgroup of patients it should be used, as studies have been underpowered.

In terms of using rhGH replacement in relation to improving conception and pregnancy outcomes, several studies have been conducted, albeit with small sample

**Table 9**  
**Parameters to be Monitored in Adults With GHD on rhGH Replacement**

Metabolic variables Body composition (BMI, waist circumference) Bone mineralization (DXA scan) Cardiovascular (blood pressure, pulse rate) Fasting lipids Physical capacity Glucose metabolism (fasting glucose and hemoglobin A1c)
Quality of life Questionnaires (QoL-AGHDA)
Assessment for side effects, and performing baseline and periodic MRIs before and after starting rhGH therapy in patients with post-surgical tumor remnant in the hypothalamic-pituitary region <sup>a</sup>
Serum IGF-1 monitoring <sup>a</sup>
Assessment and management of other pituitary hormone deficiencies <sup>a</sup>

Abbreviations: BMI = body mass index; DXA = dual-energy X-ray absorptiometry; GHD = growth hormone deficiency; IGF-1 = insulin-like growth factor-1; QoL-AGHDA = quality of life in adult growth hormone deficiency assessment; rhGH = recombinant human growth hormone.

<sup>a</sup>These items are required for safety monitoring and should be assessed regularly.

sizes. Giampietro et al (220) reported 4 cases of infertility in women with isolated GHD and normal pituitary-gonadal axis function in which rhGH replacement therapy improved dysmenorrhea and led to successful conception and pregnancies. A retrospective study of 25 women with GHD who underwent pregnancy without rhGH replacement therapy found that untreated GHD during pregnancy was not detrimental to the fetus (221), while another study of 4 women with GHD found that after discontinuing rhGH when pregnancy was confirmed, there were no pregnancy complications and healthy babies were delivered (220). In one case report of a normal pregnancy and a healthy fetus, rhGH replacement was continued until there was sufficient placental GH production (222). Others have proposed maintaining rhGH replacement during the first trimester, decreasing the dose during the second trimester, and discontinuing it during the third trimester; this has also been associated with successful pregnancy outcomes (223). In the largest series published using data derived from the Pfizer Kabi International Metabolic Surveillance (KIMS) database of 201 pregnancies from 14 European countries and the U.S., Vila et al (224) reported that nearly all women with GHD taking rhGH replacement continued treatment during the time they sought fertility. Nearly one third of patients continued treatment throughout the pregnancy, and rhGH therapy did not appear to affect pregnancy outcomes. Recently, Correa et al (225) prospectively evaluated the outcomes of fertility treatment in 5 women with CO-GHD, confirming that adequate hormone replacement, including for GHD, led to good pregnancy outcomes. However, because the data remain inconsistent in terms of the role of rhGH replacement during conception and continuation during pregnancy, until further safety data involving larger patient numbers become available, continuation of rhGH use for conception and pregnancy cannot be routinely recommended.

#### **Q10. WHAT ARE THE SIDE EFFECTS OF rhGH REPLACEMENT?**

The majority of side effects of short-term GH replacement therapy are related to sodium and water-retaining properties and reduction in insulin sensitivity, whereas long-term concerns are mainly related to the potential induction of cell growth and proliferation in response to GH and IGF-1, raising the theoretical possibility of increased risk of tumor recurrence and de novo neoplasia.

Early studies used weight-based GH-dosing regimens, resulting in high daily doses of GH in patients with high body weight and more frequent side effects that included peripheral edema, arthralgia, myalgia, muscle stiffness, carpal tunnel syndrome, paresthesia, and worsening glucose tolerance (42-44). These effects are usually seen in obese and older patients, and generally respond to dose reduction or cessation of therapy altogether. The most serious side effect is benign intracranial hyperten-

sion presenting with symptoms of papilledema and headaches, which has been reported in children (226-229), but rarely in adults (230). In summary, minimizing the risk of side effects is recommended by avoiding high rhGH doses and maintaining target serum IGF-1 levels within the age-adjusted laboratory reference range (IGF-1 SDS between -2 and + 2).

#### **Q11. HOW SAFE IS LONG-TERM rhGH REPLACEMENT THERAPY?**

The safety of rhGH replacement therapy can be improved by selecting an appropriate dose to minimize the risk of inducing side effects. Symptoms of over-replacement are less common with the use of low, fixed, nonweight-based dosing, followed by gradual upward dose titrations based on maintaining serum IGF-1 levels in the normal range. Long-term safety concerns have included risks for development or worsening of glucose intolerance or DM, theoretical concerns about neoplasia, tumor recurrence, or residual tumor growth, and effects of rhGH replacement on cardiovascular morbidity and mortality. A literature review by Stochholm et al (231) using PubMed, EMBASE, and Google Scholar to identify all relevant safety data from manufacturers' GH registries published between 1988 and 2016 provided reassuring mortality data in children and adults treated with long-term rhGH replacement therapy. Additionally, the risk of stroke, new malignancy, leukemia, extracranial tumors, or recurrence of intracranial malignancy was not increased in patients without risk factors (231). Conversely, the risk of SN, particularly in those who had received cranial irradiation was increased (231). In these patients, treatment with rhGH should be conducted with caution and monitored closely during follow-up. In a systematic review by Kokshoorn et al (232) of 534 GH-deficient patients aged 60 to 80 years, treatment with rhGH decreased LDL-cholesterol levels and improved QoL, but other parameters were unchanged. Because data about the effects of rhGH replacement in patients >80 years of age are scarce, the efficacy and safety of long-term rhGH replacement in octogenarians with GHD remain unclear. In these patients, it is recommended that treatment with rhGH be based on each individual circumstance, such as pre-existing risk factors and underlying comorbidities as well as efficacy.

##### **Q11.1. Is there a risk of worsening glycemic control with rhGH replacement?**

Untreated adults with GHD are predisposed to increased insulin resistance (233) and multiple features that resemble metabolic syndrome, which carries an increased risk of development of DM (234-236). Recombinant human GH replacement induces beneficial effects on body composition, forming a rationale for improvement in insulin resistance with treatment, and dyslipidemia. Concerns

for the development of DM in GHD patients treated with rhGH replacement therapy stem from early studies demonstrating a 6-fold relative risk of developing DM in treated pediatric GHD compared with untreated patients (237), increased prevalence of DM among participants in the KIMS database studies compared with reference populations (3,40), as well as reports of DM developing during long-term surveillance of rhGH therapy (238). Notably, no increase in prevalence or incidence was observed in treated patients in the Hypopituitary Control and Complications Study (HypoCCS) when accounting for BMI, age, and gender (39). With conflicting results in the literature, the overall effect of rhGH replacement on the development of DM is unclear. Evaluation of prospective studies indicates that shorter-term GH replacement can adversely affect glucose metabolism; conversely, low-dose rhGH replacement improves (31,239,240) or normalizes insulin sensitivity that may be related to the reduction in total body fat mass (241).

Recent systematic reviews and meta-analyses have evaluated the safety of rhGH treatment in relation to glucose metabolism. A review of 27 studies with a mean of 166 patient years demonstrated a range of DM prevalence of 0 to 16.9%, with the highest among patients with treated Cushing disease (41,242). Six studies selected in the systematic review were randomized placebo-controlled studies, 2 studies analyzing the same cohort compared treated and untreated patients, and 4 studies compared treated patients with reference populations. A trend toward an increase in incidence of DM during the first year of treatment was found. Traditional risk factors such as age and BMI were noted to be associated with an increased risk of DM, but there was no association of risk of DM with the dose of rhGH (41). By contrast, a systematic review on the safety of rhGH treatment with regard to glucose metabolism found that 3 out of the 5 studies showed an increased risk for DM (243). The investigators of this study concluded that inconsistent evidence on the development of DM may stem from the international nature of large datasets and the heterogeneity of both treated subjects and control groups.

If DM and glucose intolerance develop during rhGH therapy, or if rhGH therapy is considered in patients with pre-existing DM, addition and/or adjustments with anti-diabetic medications and use of low-dose rhGH therapy are suggested. Alternatively, it is also reasonable to withhold or discontinue rhGH therapy and to focus on optimizing antidiabetic therapy to achieve optimal glycemia first before considering to resume rhGH replacement in these patients.

#### **Q11.2. Are there risks of tumor recurrence and malignancy induced by rhGH replacement?**

Risk of malignancy in the treatment of adults with GHD is a theoretical concern given the known growth-

promoting effects of GH and IGF-1. The FDA approval of rhGH replacement for adults listed active malignancy as a contraindication. Considering that many patients with GHD have been treated for primary malignancies such as leukemia and lymphoma, or for benign intracranial tumors such as pituitary adenoma, craniopharyngioma, and meningioma, it is prudent to consider the underlying risks of tumor recurrence in these patients without rhGH use. Since SN are known to occur in some patients (244,245), especially in those irradiated for the primary malignancy, the potential risks of worsening or accelerating the course of these malignancies should be weighed against the benefits of treatment with rhGH.

It is important to recognize that tumors may recur in patients not treated with rhGH. Studies reporting recurrence risk of pituitary adenomas are highly variable in methodology. In a structured review and meta-analysis of 143 studies comprising over 17,000 patients, a variation in the overall recurrence rates across tumor subtypes was observed in patients with prolactinoma, nonfunctioning adenomas, acromegaly, and Cushing disease ranging from 0.034, 0.022, 0.007, and 0.023 patients/years, respectively (246). Paradoxically, this study demonstrated that patients with acromegaly had fewer recurrences than patients with other pituitary adenomas, implying the lack of effect of chronic excess GH exposure to tumor recurrence.

A retrospective analysis of the HypoCCS population evaluated the risk of primary cancers, and the recurrence rates of pituitary tumors and craniopharyngiomas (247). Comparisons were made between 8,418 rhGH-treated and 1,268 untreated patients, along with comparisons with regional rates of neoplasia. With a mean follow-up period of 4.8 years, there was no increase in primary cancers in patients treated with rhGH, with special attention to breast (standardized incidence ratio [SIR]: 0.59, CI: 0.36 to 0.90), prostate (SIR: 0.80; CI: 0.57 to 1.10), and colorectal cancers (SIR: 0.62, CI: 0.38 to 0.96). They also reported no increase in the recurrence of pituitary adenoma relative risk (RR) 0.91 (CI: 0.68 to 1.22) and a nonstatistically significant increase in craniopharyngioma recurrence in rhGH-treated patients with an RR of 1.32 (CI: 0.53 to 3.31).

The risk of an SN has been evaluated in several multi-institutional retrospective cohorts. Childhood cancer survivors enrolled in GeNeSIS (Genetics and Neuroendocrinology of Short Stature International Study) pediatric and HypoCCS adult observational studies of rhGH treatment were assessed for the incidence of SN in GH-treated compared with nonGH-treated patients. The percentage of childhood cancer survivors treated with rhGH who developed an SN was 3.8% in pediatric GeNeSIS participants and 6.0% in adult HypoCCS participants, whereas the estimated cumulative incidence of SN at 5 years of follow-up was 6.2% and 4.8%, respectively. The incidence of SN in GeNeSIS and HypoCCS rhGH-treated participants is similar to the published literature and was consistent with increased risk of SN in childhood cancer

survivors treated with GH (245). Conversely, Brignardello et al (248) reported an elevated risk of SN that was more likely to be related to previous exposure to irradiation therapy than rhGH replacement because the cumulative incidence of SN did not differ according to whether rhGH replacement was administered or not.

There have also been other studies that have supported the favorable safety profile of rhGH therapy, and SN, cancer and intracranial tumor recurrences in children with growth disorders. Patterson et al (249) analyzed data from the Childhood Cancer Survivor Study including 12,098 pediatric cancer survivors diagnosed with cancer prior to age 21 years, of whom 338 were treated with GH, and found that the development of meningioma, glioma, and other SN was unrelated to rhGH replacement. In a prospective observational study, Hartman et al (250) found that after a mean follow-up of 2.3 years, there was no significant difference in the rates of intracranial tumor growth or recurrence in GH-treated compared with untreated childhood cancer survivors. A systemic review and meta-analysis by Tamhane et al (251) also demonstrated no increases in the occurrence of SN or recurrence in childhood cancer survivors, whereas Krzyzanowska-Mittermayer et al (252), using data derived from the KIMS database, reported an increased risk of SN in childhood-onset, but not adult-onset, cancer survivors. Radiotherapy may play a role in the occurrence of basal-cell carcinomas and in the development of second malignant tumors, but the role of rhGH replacement remains unclear, prompting the recommendation for lifelong follow-up of cancer survivors. In a prospective, multinational, observational study (Genetics and Neuroendocrinology of Short Stature International Study) of 22,311 children, Child et al (253) demonstrated that rhGH therapy did not increase the overall risk of death or primary cancer. Conversely, in a meta-analysis performed by Li et al (254) to evaluate the risk of cancer in adults, these investigators found that rhGH replacement therapy was associated with a decreased risk of cancer in adults with GHD (RR = 0.69, 95% CI: 0.59 to 0.82).

Currently, there are also no studies that have specifically addressed the optimal interval between completion of cancer therapy and initiation of rhGH treatment in patients with a history of cancer. The 2003 Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee (255) and the 2018 Endocrine Society CPG (123) have proposed waiting for at least 1 year of being disease-free after completion of childhood cancer treatment before considering rhGH therapy. Such therapy should be considered based on individual circumstances and after discussions with the patient's oncologist. In parallel, regular tumor screening and imaging studies, according to available CPG, are prudent despite the lack of evidence to support this practice.

Other factors to consider when deciding on the timing of initiation of rhGH therapy include primary tumor type, overall oncologic prognosis, risk of relapse, severity of

symptoms of GHD, and the goals of the patient. Since cancer survivors (especially adult survivors with childhood cancer) show a modest risk of developing SN, the different goals of using GH replacement to induce linear growth in children versus reversing metabolic and psychologic abnormalities in adults should be clearly communicated to the patient before deciding whether to commence rhGH replacement therapy in adulthood. For older (256) and obese (257) adults in whom indolent cancers are more prevalent, it is recommended to use low rhGH doses and gradually to up-titrate the dose in small increments to achieve serum IGF-1 levels no higher than +2 SDS.

For adults with GHD and a history of cancer who have specifically expressed a desire to start rhGH replacement therapy, such therapy may be considered based on each individual circumstance. Low-dose rhGH therapy should only be initiated after at least 5 years after cancer remission is achieved with the understanding that in some patients (particularly those with childhood cancers), rhGH may potentially increase the risk of SN (258). Our recommendation of the 5-year timeline is based on an abundance of caution with no qualifying data, and with the understanding that the patient's oncologist is in agreement and closely involved in follow-up care while the patient is on therapy (258). It is important to counsel the patient that definitive data on the effects of rhGH replacement and cancer risk are lacking, and specifically in adult survivors of childhood cancer, rhGH therapy may modestly increase the risk of SN, particularly if patients have received radiation therapy (231). Clearly, the beneficial effects of rhGH replacement need to be carefully balanced against the possible, yet unsubstantiated, increased cancer risk and increased morbidity in untreated adults with GHD. Notably, rhGH replacement is contraindicated if the patient has active malignancy, whereas in patients with a history of a monogenic tumor syndrome (e.g., neurofibromatosis type 1), we recommend exercising particular caution when considering rhGH use as these patients may be susceptible to developing future cancers (259,260). Conversely, consideration for treatment with rhGH should be made with caution in patients with a strong family history of cancer. Nevertheless, even after over 20 years of adult rhGH replacement, evidence suggesting that rhGH replacement in adults increases cancer risk or accelerates recurrences of tumors in the hypothalamic-pituitary region remains unclear; hence, for safety surveillance, it is important that continued long-term monitoring, including standard recommendations for cancer screening, be performed in these patients.

### **Q11.3. What are the cardiovascular effects of rhGH replacement?**

For several decades it has been well established that adults with untreated GHD have increased cardiovascular risk due to altered body composition, abnormal lipid



profile, insulin resistance, and impaired glucose metabolism. A large retrospective study of 1,411 patients with hypopituitarism not treated with rhGH found increased overall mortality, myocardial infarctions, and cerebrovascular events compared to the normal population (261). The same study evaluated patients treated with rhGH and found similar rates of overall mortality to the normal population and lower rates of myocardial infarction (261). Conventional cardiovascular risk markers such as dyslipidemia, insulin resistance, and glucose intolerance, and the presence of features of the metabolic syndrome (elevated blood pressure, increased central adiposity) are all well-known features associated with adult GHD (1-3). Other surrogate markers for cardiovascular risk have been reported to be associated with GHD, such as increased serum levels of C-reactive protein (CRP) (262,263), pro-inflammatory cytokines (263), adipokines (264,265), adiponin (266), pregnancy-associated plasma protein A (267,268), oxidative stress (263), coagulation system (269,270), and endothelial dysfunction (263). Recombinant human GH replacement in adults with GHD exerts positive effects on some cardiovascular risk markers (271-273) and has been shown to lower Framingham, Prospective Cardiovascular Münster Heart Study, and European Society of Cardiology Score algorithms with male sex, high total and low HDL-cholesterol levels being potential predictors of good response (274), but long-term controlled trials evaluating the effects of GH replacement on cardiovascular morbidity and mortality are still lacking (275).

Standard lipid profiles improved with rhGH therapy, with studies demonstrating lower total cholesterol (16,208,238,276-282), decreased levels of LDL cholesterol (16,208,238,277-280,282,283), and unchanged triglyceride levels (16,208,238,277,278,280,282-284). Similarly, other cardiovascular risk factors such as CRP (271,285), pro-inflammatory cytokines such as interleukin-6 and tumor-necrosis factor alpha (286,287), pregnancy-associated plasma protein A (268), and lipid peroxidation (288) decreased following rhGH therapy. Recombinant human GH replacement has also been associated with improvements in markers of endothelial dysfunction (289) and positive effects on left ventricular mass, intraventricular septum, diastolic function, and stroke-volume index (290).

Adults with hypopituitarism demonstrate increased mortality, mainly due to cardiovascular and cerebrovascular events (8,59,291,292). Increased mortality is more pronounced in women than men (male standard mortality ratio 2.06; 95% CI 1.94 to 2.2 versus female standard mortality ratio 2.80; 95% CI 2.59 to 3.02) (293). Studies in the modern era of pituitary hormone treatment, including more refined surgical, radiotherapy, and medical treatment techniques suggest a normalization of mortality when rhGH is replaced in men and an improvement, but not normalization, in the standard mortality ratio in women (6,55,56).

## Q12. IS rhGH RECOMMENDED FOR SPORTS?

In the sporting arena, the enormous financial gains and fame that successful athletes can accrue have led some to resort to extraordinary lengths to win. While rhGH replacement is effective in treating GH-deficient patients, its theoretical effects on the musculoskeletal and other systems have made it an attractive drug for abuse in sports. Increasingly used by athletes, rhGH is a banned substance for competitive sports by the World Anti-Doping Agency (WADA) in its 2019 Prohibited List of substances (294). It is important to note that prescribing rhGH for athletic enhancement is illegal. Amateur athletes and young adults who seek to enhance their athletic skills or to improve their physiques also represent an increasing population of healthy, GH-sufficient people who are taking rhGH for unapproved uses (295,296). Because testing to detect GH abuse is not standardized across all sports, the prevalence of this abuse can be surmised only through anecdotal evidence.

Claims that rhGH enhances physical performance are not supported by the scientific literature. Although limited evidence suggests that rhGH increases lean body mass and sprint capacity (297), it may not improve strength (298) and in fact may worsen exercise capacity and increase the incidence of adverse events (298,299). In a meta-analysis of published studies on the effects of rhGH administration on body composition, substrate metabolism, and athletic performance in 254 healthy, young subjects, rhGH administration was found to induce significant changes in body composition but did not increase either muscle strength or aerobic exercise capacity (299). Recombinant human GH is used in this setting to capitalize on its anabolic and lipolytic properties (300); however, endocrine profiles differ between sports in elite athletes (301). There are also differences between how elite athletes and clinical investigators measure the potential benefit of a medication. Highly trained athletes are keenly aware of their performance and evaluate small improvements in response to changes in training. In addition, athletes typically combine rhGH with other drugs that are individually tailored to their preferences, whereas clinical trials are designed to evaluate relatively large changes between groups of subjects making only 1 or 2 interventions at a time with all other variables being kept equal.

The anabolic actions of GH are mostly mediated through IGF-1 and include increases in total body protein turnover and muscle synthesis, as seen in adults with GHD and endurance-trained athletes (302). Growth hormone alone stimulates proliferation of cartilage in the growing epiphyseal plate, stimulates linear growth, increases bone mass and mineral content (303), and promotes lipolysis in adipose tissue, leading to a net reduction in fat mass (304). When combined with testosterone, rhGH can exert synergistic effects on anabolism (305,306); athletes frequently



combine these hormones, seeking to gain maximal effects to enhance their performance.

### **Q12.1 What are the challenges of detecting rhGH abuse?**

Important considerations when measuring serum GH levels for antidoping purposes include the amino acid–sequence identity between the main fraction of pituitary-derived GH and rhGH, the heterogeneous nature of GH, the presence of GH-binding proteins in plasma, the potential cross-reactivity with homologous polypeptide hormones, the heterogeneous immunoreactivity of (monoclonal) antibodies used for commercial immunoassays, and the short half-life of GH in circulation.

Detecting abuse of rhGH poses many challenges. Unlike many other abused substances, such as synthetic anabolic steroids, GH is a naturally occurring substance and has a short half-life of 4 hours after subcutaneous injection and only 22 minutes after intravenous injection. Thus, demonstration of exogenous administration must rely on the detection of concentrations exceeding established reference intervals at the appropriate time after administration. Ideally, testing should be undertaken within 12 to 24 hours after the last rhGH dose to give the best chance of detection (307). Other physiologic challenges include the pulsatile release pattern of GH, and the fact that serum GH levels normally increase 2 hours after exercise (308,309). Although investigators can perform repeated sampling over 24 hours to overcome the issue with pulsatility, this is neither practical nor feasible in the sports setting.

Traditional drug testing in sports has involved urine sampling, but this is not viable for rhGH detection because neither GH itself nor markers of GH, which are also peptides, are secreted into the urine in sufficient and reliable quantities (310). Consequently, blood sampling is required for the detection of rhGH abuse, although more recently, alternatives such as dried blood spots, dried plasma spots, oral fluid, exhaled breath, and hair have been studied (311). This is minimally invasive and has been accepted for use in competitive events for blood doping and erythropoietin detection.

### **Q12.2. What are the biomarkers to detect rhGH abuse?**

The anabolic actions of rhGH administration lead to the generation of several proteins in the liver and other tissues. The serum concentrations or ratios of these proteins can be used as biomarkers for detecting exogenous rhGH use. Two groups of biomarkers were previously identified by the GH-2000 Research Team to detect subjects receiving exogenous rhGH: one group of biomarkers includes members of the IGF-IGFBP axis, and the other includes markers of bone and collagen turnover and mineraliza-

tion (312). IGF-1 has little diurnal or day-to-day variation, increases 1.3- to 2.3-fold in a uniform dose-dependent fashion after rhGH administration (313), and undergoes minimal change with exercise. Similarly, several bone and soft-tissue markers change in response to rhGH administration. Procollagen III terminal peptide is a marker of type-3 collagen formation (mainly soft tissues), exhibits little day-to-day, diurnal, or gender variation in basal concentrations and increases in a dose-dependent fashion after rhGH administration (312), whereas C-terminal cross-linked telopeptide of type-I collagen has been shown to be a sensitive marker of bone resorption (314).

Another approach using biomarkers to detect rhGH abuse in sports is to measure serum GH isoforms (315). Endogenous GH exists in the 22-kd isoform (constituting 75% of circulating GH) and other forms (“non-22-kd”) that include the 20- and 17-kd isoforms (316). Exogenous administration of rhGH, which contains only the 22-kd isoform, suppresses endogenous GH secretion and increases the ratio of 22-kd to 20-kd of GH (317). Currently, there are 2 approaches used by WADA-accredited laboratories for detection of GH abuse in sports, namely the GH isoform test (318) and the GH biomarkers test (319). The isoform test is based on 2 immunoassays that distinguish between the 22-kd GH isoform and all other endogenous GH isoforms using specific monoclonal antibodies (320). Administration of exogenous rhGH increases the concentration of the 22-kd GH isoform only, disrupting the ratio of 22-kd isoform to all pituitary isoforms, which allows identification of rhGH abuse in athletes. Although this direct isoform-detection method is technically robust, it has some limitations, such as a narrow window for detection (up to 36 hours after the last injection depending on the administered dosage concentration and athlete gender) and it cannot detect potentially available purified pituitary-derived GH (321,322). The biomarkers test is an indirect method which is based on measuring increased levels of GH-responsive proteins such as IGF-1 and procollagen type-III amino-terminal pro-peptide (P-III-NP) (318,323). A major advantage of using the biomarkers test is the wider time window of detection compared to the isoform test (322). The concentrations of IGF-1 and P-III-NP markers progress at different rates after GH stimulation; the former generally increases to its maximum within 2 weeks following rhGH injection, while the latter progresses gradually and peaks within 4 to 6 weeks (324). After rhGH administration is discontinued, IGF-1 levels decrease rapidly within a week whereas P-III-NP decline more slowly, returning to baseline by 6 weeks (324). This provides an opportunity to use the biomarkers test for both “in and out of competition” stages. Despite having an advantage of a wider time window for detection, the biomarker test contains some limitations, such as the concentration of IGF-1 in circulation being very age- and gender-dependent (323) and partially sport- and exercise-dependent (325). To

address this variability, several criteria (age, gender, sport, ethnicity, etc.) need to be taken into consideration in order to identify exogenous GH administration accurately. This variability has contributed, at least in part, to the limited number of positive GH abuse cases in sports to date.

Tan et al (326) and Ferro et al (327) described apolipoprotein/APOL1, alpha-2-HS-glycoprotein (AHSG), vitamin D-binding protein (VDBP), and fibronectin as potential biomarkers to improve detection of rhGH abuse. APOL1 belongs to HDL-lipoprotein, which is expressed in the pancreas, liver, and in many other tissues (328), and has been reported that rhGH treatment has a positive correlation with HDL expression in both healthy men and women (329). AHSG is a ~40 kd protein that is synthesized and secreted by hepatocytes into the plasma, acts as a carrier protein (330), and is expressed in the pituitary gland (331). It has been shown that AHSG inhibits the action of leukemia inhibitory factor (LIF) in pituitary corticotropes (332). As overexpression of LIF leads to expansion of pituitary corticotropes and suppression of somatotropes, and as LIF inhibits GH secretion (333), an inhibitory effect of AHSG on LIF may result in stimulation of GH secretion. Because excess GH exposure induces insulin resistance, the increase in AHSG by rhGH administration may play a role in mediating this effect. VDBP is the main carrier of vitamin D metabolites, namely 25-hydroxyvitamin D3 (25OHD3) and 1,25-dihydroxyvitamin D3 (1,25[OH]2D3) in circulation (334). Previous studies reported that prolonged GH excess in acromegaly is associated with increased serum VDBP and rhGH administration in healthy men and elevates circulating VDBP (335,336). Each of these candidate biomarkers identified were overexpressed during rhGH administration (except VDBP), and their concentrations returned close to the levels in placebo-treated subjects after 1 day of washout (326). VDBP was the only candidate biomarker which was repressed due to rhGH administration and stayed low until the end of the washout period. Hence, decreasing VDBP levels offer a different measurement vector that could help strengthen the current biomarker test options that may have sports antidoping utility.

### **Q13. IS rhGH RECOMMENDED FOR ANTI-AGING?**

The widely advertised potential of rhGH as an anti-aging agent has attracted much publicity; hence, in the U.S., the distribution and marketing of human GH via internet sites and anti-aging groups are increasingly common practice. Prescribing and administering rhGH for “anti-aging” has become a routine intervention in an industry that has made claims about GH being a remedy for aging, or the so-called “fountain of youth” (337, 338). The use of rhGH for anti-aging and for athletic enhancement accounts for ~30% of GH prescriptions in the U.S. (339). It is impor-

tant to note that neither of these indications is approved by the FDA.

Despite its increasing use as an anti-aging agent, no studies have assessed long-term (>6 months) efficacy or safety of rhGH administration for this purpose. In theory, the use of rhGH might be logical to consider because aging is associated with the gradual reduction in GH secretion, and therefore it has been hypothesized that rhGH supplementation might safely arrest or reverse aging (340). A meta-analysis of 31 studies evaluating varying doses and duration of rhGH therapy in healthy elderly subjects reported small changes in body composition but significant rates of adverse events (341), while animal studies have shown reduced life spans and premature onset of age-related cognitive changes with rhGH treatment (337,338).

In the U.S., off-label distribution or marketing of rhGH to treat aging or aging-related conditions and for the enhancement of athletic performance is illegal (342). Physicians and other health-care professionals must be aware that under no circumstances should rhGH be prescribed unless the patient has a clearly defined indication. Given the clinical concerns and the legal issues involved, we strongly recommend against marketing, distributing, or administering rhGH for any reason other than the well-defined approved uses of the drug.

### **Q14. WHAT NEW DEVELOPMENTS ARE IN THIS FIELD?**

Recombinant human GH was originally approved in 1985 by the FDA for the daily subcutaneous injection as replacement therapy for adults with a history of hypothalamic-pituitary disease or CO-GHD confirmed to have GHD on biochemical testing. Over 2 decades later, rhGH replacement is still being administered as daily injections. This frequently poses a barrier to initiating treatment or to adherence for some patients and has been shown to result in reduced effectiveness (343,344). Because rhGH is often used for a number of years to achieve optimal growth in children and is potentially a lifelong therapy in adults with GHD, adherence is essential to the effectiveness of the therapy.

Dosing in adults on alternate days or 3 times a week has been shown to be as effective as daily dosing (345). In addition, there is no clinically notable difference in the metabolic response to once- versus twice-daily subcutaneous rhGH (346), or to continuous intravenous rhGH infusion (347). As the frequency of injections is thought to be one of the factors contributing to nonadherence to rhGH therapy in adults with GHD (348), a lower frequency dosing schedule would be potentially less burdensome to patients and may improve adherence to treatment. A number of companies have been developing LAGH preparations that are administered less frequently than daily injections, and several different methods are used to render

the human GH molecule long-acting (349-351). The 5 general categories of LAGH preparations that have been studied include depot formulations, pegylated molecules, prodrug compounds, GH molecules noncovalently bound to albumin, and GH fusion proteins. While a number are no longer being developed, currently there are still several LAGH preparations in various stages of clinical trials and some have been approved in at least one country, but none are available yet in the U.S. (352-354). As LAGH preparations will likely gain approval by regulatory authorities in the coming years, it is important to acknowledge the following questions that will require clarification:

- i. What are the long-term metabolic consequences and cancer risks of prolonged elevation of serum GH levels in the circulation?
- ii. If side effects occur using LAGH preparations, will they be prolonged?
- iii. Since LAGH preparations are composed of large molecules, will these sizes decrease their ability to penetrate all tissues with GH receptors and cause differing effects from daily rhGH injections?
- iv. Will the effects of LAGH preparations be durable with long-term use?
- v. Will LAGH preparations be a cost-effective alternative to daily rhGH injections?
- vi. Will LAGH preparations truly improve adherence rates and efficacy compared to daily rhGH?

#### **Q14.1. Are long-acting GH preparations safe and effective?**

Questions have arisen as to whether LAGH preparations would be as safe and efficacious as daily administration, but these concerns have not been borne out by any hard evidence thus far. The present method of daily rhGH administration in clinical use is already unphysiologic compared to the very fine-tuned and complex regulation of endogenous GH secretion seen in healthy individuals, and LAGH preparations would be even less physiological in nature. Nevertheless, it is noteworthy that there are several hormones administered as commercially available long-acting formulations that do not mimic normal pulsatile physiology, such as testosterone, medroxyprogesterone, and gonadotropin-releasing hormone. Additionally, other types of medications frequently used by endocrinologists have been developed as long-acting preparations, such as once or twice weekly cabergoline rather than once-to-three times daily bromocriptine for hyperprolactinemia, bi-weekly testosterone cypionate injections rather than daily transdermal testosterone applications, and ultra-long-acting antiresorptive medications, such as annual intravenous zoledronic acid infusions rather than once-daily or once-weekly oral alendronate for osteoporosis.

It is likely that LAGH preparations, provided they meet the criteria of noninferiority in efficacy, safety, and

convenience, will prove to be a positive addition to the present armamentarium in the management of children and adults with GHD, particularly as many patients are expected to prefer less frequent injections. Studies on LAGH preparations that were reported recently support this notion (349,351,354-357), demonstrating comparable efficacy and safety to daily rhGH preparations. Notably, long-term surveillance registries will be essential to assess for long-term efficacy, safety, tolerability, cost-effectiveness, and to improve our understanding of the effects of prolonged exposure to these compounds (349).

#### **Q14.2. How will the doses of long-acting GH preparations be adjusted?**

Serum IGF-1 remains the best currently available biomarker for GH action and will be used to monitor therapy with LAGH preparations. However, the optimal timing of measurement of serum IGF-1 levels in relation to the medication injection is unclear. Nonetheless, there is general agreement that serum IGF-1 levels should not be supraphysiologic for a prolonged period of time (349-351), as this might induce unwanted "iatrogenic acromegaly." Additionally, because daily rhGH injections rapidly result in stable serum IGF-1 levels, measurement of this hormone at any given time during therapy has been used to guide dosing. However, with weekly rhGH administration, serum IGF-1 levels will inevitably show more variability and changes across the days between injections. It remains to be determined whether a dose of LAGH preparation should be titrated based on the nadir, peak, or mean values of serum IGF-1 levels during treatment. It should also be emphasized that there remains an unmet need for better biomarkers for monitoring rhGH therapy with the expected introduction of LAGH preparations (349).

The GH Research Society held a workshop in November, 2015, on LAGH preparations and concluded that these compounds will offer convenience and may have the potential for increased adherence and improved outcomes. Further investigation, including long-term surveillance studies after any regulatory approvals, was advised with the objective of assessing for long-term efficacy, safety, tolerability, and cost-effectiveness and to help better understand the effects of prolonged exposure to these compounds (349). It is suggested that endocrinologists monitor developments in this field as FDA submission(s) may occur in the next few years.

### **Q15. CONCLUSION**

Untreated adults with GHD are associated with excess morbidity and mortality, mainly from cardiovascular disease. With appropriate dosing of rhGH replacement, many features of adult GHD are reversible and side effects of therapy can be minimized. The diagnosis in adults is

often challenging because of the lack of a single biologic end-point, hence GH-stimulation test/s are recommended. The decision to test for adult GHD should be based on the appropriate clinical context of each individual patient with a reasonable probability of GHD. Currently available GH-stimulation tests have several caveats, including intra-individual variability, different peak GH cut-points depending on which test is used, relative lack of validated normative data based on age, gender, and BMI, and paucity of data for specific subpopulations of adults with GHD. With the removal of recombinant GHRH (sermorelin acetate for injection) from the U.S. market in 2008, the GST has been increasingly used based on its availability, reproducibility, safety, lack of influence by gender and hypothalamic cause of GHD, and relatively few contraindications. Macimorelin, a drug administered orally, was approved by the U.S. FDA in December, 2017, and appears to be a very promising test that is easy to conduct with high reproducibility, safety, and diagnostic accuracy comparable to the ITT and GHRH plus ARG test. Once the diagnosis of adult GHD is established, rhGH should be initiated at low doses and uptitrated with close attention to avoid over-treatment and side effects. Periodic monitoring is imperative for both side effects and physiologic benefits.

Recombinant human GH therapy consistently has been shown to be beneficial for adults with GHD, including improvements in body composition, muscle strength, skeletal integrity, lipid profile, and QoL. In addition, rhGH therapy has been shown to improve many cardiovascular surrogate biomarkers such as lipid profile, CRP, interleukin-6, tumor-necrosis factor alpha, and pregnancy-associated plasma-protein A. Despite these positive effects, improvement in overall cardiovascular mortality with rhGH replacement therapy in patients with hypopituitarism has not definitively been proven in long-term prospective, controlled clinical trials, and realistically, it is unlikely that such trials can be feasibly conducted. The small number of subjects with rhGH treatment data and absence of long-term results for clinical endpoints such as fractures, cardiovascular disease, cancer and mortality in an adequate control population remain a limitation; therefore, caution is needed when interpreting these data. However, based on available published literature, short- and long-term GH replacement in adults with GHD is safe. There are currently several ongoing studies of LAGH preparations that use a variety of technologies to prolong GH action, and it will be interesting to monitor developments in this area, as these compounds offer the possibility of better adherence and treatment efficacy.

## DISCLOSURE

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*Note: Reference sources are followed by an evidence level (EL) rating of 1, 2, 3, or 4. The strongest evidence levels (EL 1 and EL 2) appear in bold for easier recognition.*

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