Guideline-Recommended Diagnosis and Coding of Growth-Related Disorders in Children and Adults in the Managed Care Setting

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Talking Points

- Review the 2009 update of the *AACE Medical Guidelines for Growth Hormone Use in GHD Adults and Transition Patients*
- Review and differentiate the diagnostic criteria for SGA and ISS
- Identify available devices for rhGH administration and review their role in promoting adherence to GH therapy

GHD=growth hormone deficient
SGA=small for gestational age
ISS=idiopathic short stature

AACE=American Association of Clinical Endocrinologists
rhGH=recombinant human growth hormone

Perspective

- rhGH is effective and safe for improving adult height and metabolism in patients with GHD as well as those with genetic syndromes associated with short stature[1]
- Patients with ISS and children born SGA can achieve normalization of adult height with GH supplementation[1]
- Diagnosis must take into account the underlying causes of GHD and short stature[1-3]
- Treatment guidelines provide parameters for GH therapy[2]
- Desired clinical outcomes and patient expectations should be considered when making treatment decisions[1-3]

1. Hardin DS, et al. *Clin Pediatr (Phila)*. 2007;46(4):279–286.
2. Cook DM, et al. *Endocr Pract*. 2009;15(Suppl 2):1–29.
3. Cohen P, et al. *J Clin Endocrinol Metab*. 2008:93(11):4210–4217.

AACE Medical Guidelines for Growth Hormone Use

AACE 2009: Background

- 2003 AACE guidelines identified the benefits of GH replacement in adults with GHD including[1]
  - Increased bone density and lean tissue; decreased adipose tissue
  - Enhanced exercise capacity
  - Improved mood and motivation
  - Concerns over misuse of GH in non-medical conditions (ie, sports and aging) motivated a revision of the Guidelines in 2009[2]

1. Gharib H, et al. *Endocr Pract*. 2003;9(1):64–76.
2. Cook DM, et al. *Endocr Pract*. 2009;15(Suppl 2):1–29.

AACE 2009: Background *(cont.)*

- Considerable variability in the clinical practice of GH replacement for adults with GHD due to[1]
  - Limited awareness of how to appropriately diagnosis adult GHD
  - Concerns about long-term risk
  - Need for daily injections
  - High cost of therapy

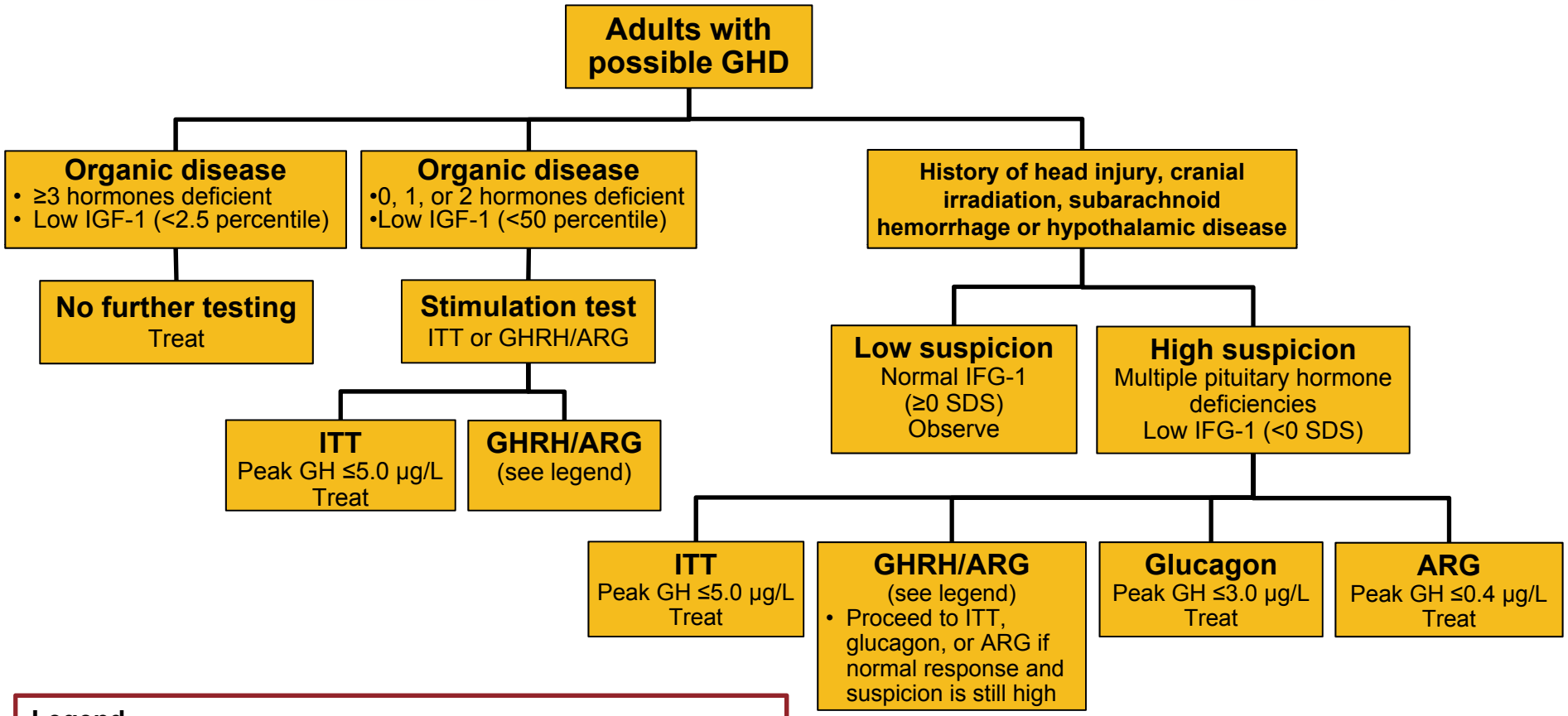
1. Cook DM, et al. *Endocr Pract*. 2009;15(Suppl 2):1–29.

AACE 2009: Managing the Transition From Child-Onset to Adult GHD

- Patients with childhood-onset GHD previously treated with GH should be retested after final height achieved
  - Preferred GH stimulation test is the insulin tolerance test
  - Acceptable alternatives include the growth hormone releasing hormone + arginine test, the glucagon test, and (rarely), the arginine test alone
- No proven benefit to continuing GH treatment into adulthood except for GHD-related conditions (eg, Turner's syndrome, idiopathic short stature)

Cook DM, et al. *Endocr Pract*. 2009;15(Suppl 2):1–29.

AACE 2009: Diagnosis of Adult GHD



Legend
Treat if peak GH ≤11.0 µg/L in patients with BMI <25 kg/m^2, peak GH ≤8.0 µg/L in patients with BMI ≥25 and <30 kg/m^2, or peak GH ≤4.0 µg/L in patients with BMI ≥30 kg/m^2

IGF-1=insulin-like growth factor 1
ITT=insulin tolerance test
GHRH=GH releasing hormone
ARG=arginine

Cook DM, et al. *Endocr Pract*. 2009;15(Suppl 2):1–29.

AACE 2009: Diagnosis of Adult GHD

Includes patients with irreversible hypothalamic-pituitary structural lesions and evidence of hypopituitarism

Adults with possible GHD

Organic disease
- ≥3 hormones deficient
- Low IGF-1 (<2.5 percentile)

No further testing
Treat

Organic disease
- 0, 1, or 2 hormones deficient
- Low IGF-1 (<50 percentile)

Stimulation test
ITT or GHRH/ARG

ITT
Peak GH ≤5.0 µg/L
Treat

GHRH/ARG
(see legend)

History of head injury, cranial irradiation, subarachnoid hemorrhage or hypothalamic disease

Low suspicion
Normal IFG-1
(≥0 SDS)
Observe

High suspicion
Multiple pituitary hormone deficiencies
Low IFG-1 (<0 SDS)

ITT
Peak GH ≤5.0 µg/L
Treat

GHRH/ARG
(see legend)
- Proceed to ITT, glucagon, or ARG if normal response and suspicion is still high

Glucagon
Peak GH ≤3.0 µg/L
Treat

ARG
Peak GH ≤0.4 µg/L
Treat

Legend
Treat if peak GH ≤11.0 µg/L in patients with BMI <25 kg/m^2, peak GH ≤8.0 µg/L in patients with BMI ≥25 and <30 kg/m^2, or peak GH ≤4.0 µg/L in patients with BMI ≥30 kg/m^2

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GHD may be transient in these patients; therefore, GH stimulation testing is recommended at least 12 months after the traumatic event

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GHRH/ARG
(see legend)

ITT remains the gold-standard test for diagnosing adult GHD

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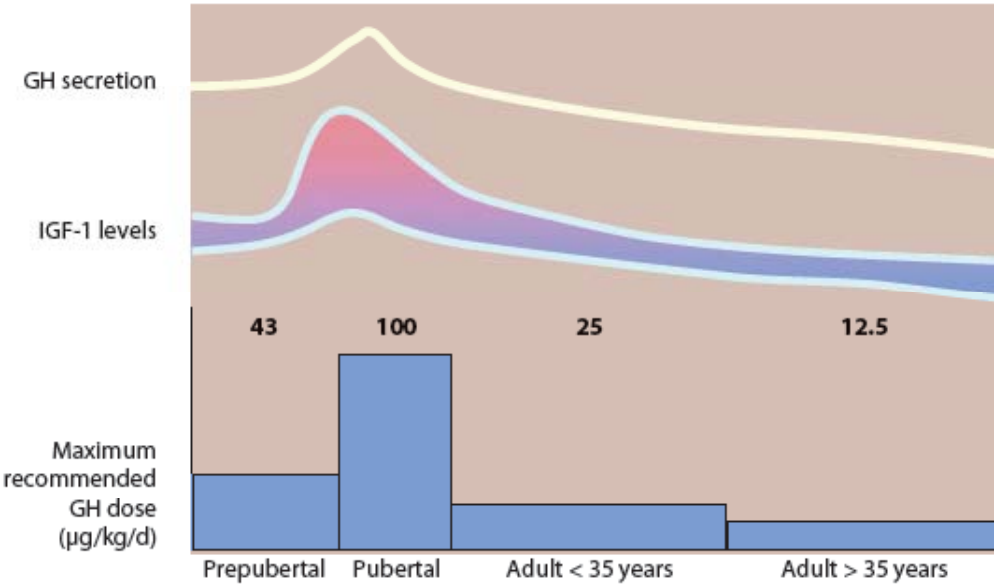
GH Dosing Is Generally Based on Normal Physiologic Patterns of GH Secretion

- Recombinant GH approved by the FDA in 1996 for use as replacement therapy in GHD[1]
- A lack of consensus persists regarding the optimal approach to dosing GH[1]

Timeline of GH Secretion[2]



1. Cook DM, et al. *Endocr Pract*. 2009;15(Suppl 2):1–29.
2. Brabant G, et al. *Horm Res*. 2003;60(2):53–60.

AACE 2009: General GH Dosing Guidance for Adults With GHD

- Dosing should be individualized independent of body weight
  - Goal is to normalize serum IGF-1 levels without causing AEs
    - Aim for serum IGF-1 levels in the middle of the normal range appropriate for age and sex, unless side effects are significant
  - A higher dose can be considered to determine whether it provides further benefit*
- For patients with adherence issues, administer on alternate days or 3x/week (using the same total weekly dosage)

***As long as the serum IGF-1 levels remain within the normal range and the patient does not experience side effects.**

Cook DM, et al. *Endocr Pract*. 2009;15(Suppl 2):1–29.

AACE 2009: GH Replacement Recommendations in Adults With GHD

- Starting dose
  - <30 years: 0.4–0.5 mg/d (or higher when transitioning from pediatric treatment)
  - 30–60 years: 0.2–0.3 mg/d
  - >60 years: 0.1–0.2 mg/d
  - Lower doses (0.1–0.2 mg/d) if diabetes/glucose intolerance present
- Dose titration
  - Increase 0.1–0.2 mg/d at 1- to 2-month intervals, depending on clinical response, serum IGF-1 levels, side effects, and comorbidities (eg, diabetes, etc.)
  - Longer intervals and smaller dose increments may be necessary in older patients

Cook DM, et al. *Endocr Pract*. 2009;15(Suppl 2):1–29.

AACE 2009: GH Replacement Recommendations in Adults With GHD *(cont.)*

- Monitoring
  - Assess clinical response, side effects, serum IGF-1, and fasting glucose levels at 6-month intervals
  - Measure quality of life (QoL) and lipids every 6–12 months
  - Evaluate bone density every 2–3 years
- Duration of therapy
  - Appropriate length of therapy is unclear; continue treatment if benefits are achieved
  - If objective benefits not achieved after 2 years, consider discontinuation

Cook DM, et al. *Endocr Pract*. 2009;15(Suppl 2):1–29.

AACE 2009: Safety of GH Replacement in Adults With GHD

- Contraindications include history or presence of malignancy
- Patient with diabetes may require low dose GH and/or an adjustment of diabetes medications
  - Patients should optimize glucose control before GH treatment
- Only limited data available regarding cardiovascular morbidity in GHD
  - Observation that rate of MI is lower in patients on GH replacement therapy implies that GH replacement therapy may reduce CV risk

Cook DM, et al. *Endocr Pract*. 2009;15(Suppl 2):1–29.

AACE 2009: Statements on Unapproved Use of GH in Adults

- Use of GH for nonmedical conditions is strongly discouraged
- Rationale for use outside of approved indications
  - Anabolic actions of GH lead to its abuse in sports
  - Supplement age-related decrease in GH secretion
- Approximately 30% of GH Rx in the US are for anti-aging and athletic enhancement

Cook DM, et al. *Endocr Pract*. 2009;15(Suppl 2):1–29.

AACE 2009: Summary of Treatment Recommendations of Adult GHD

- GHD is a well-recognized clinical syndrome in adults
- GHD is associated with significant comorbidities if untreated
- Only patients with documented hypothalamic-pituitary disease and/or biochemically-proven GHD should be prescribed GH
- Low GH doses are recommended at initiation with gradual upward, stepwise titration
- Clinical response and adverse events should be routinely monitored
- Prescribing GH to patients for any reason other than the well-defined approved uses of the drug is not recommended

Cook DM, et al. *Endocr Pract*. 2009;15(Suppl 2):1–29.

Idiopathic Short Stature and Small for Gestational Age

Idiopathic Short Stature: Definition

- Definition
  - Height that is more than -2 SD score (SDS) below the corresponding mean height for a given age, sex, and population group without evidence of systemic, endocrine, nutritional, or chromosomal abnormalities
- Children with ISS have normal birth weight and are not GH deficient
  - However, GHD must be excluded to make a diagnosis of ISS

Criteria for Deciding to Refer to Endocrinology for Evaluation of Short Stature

- In the presence of short stature
  - **Very Short:** height less than 2 SD below the mean
  - **Short for Family:** height more than 1.5 SD below the midparental height
  - **Short and Growing Slowly:** height <1.7 SD below the mean AND one-year height velocity <-1 SD, or a decrease in height SD >0.5 over one year
- In the absence of short stature
  - **Severe Growth Deceleration:** height velocity <-2 SD over one year or <-1.5 SD over two years or decrease in height SD >1 over two years
  - **Intracranial Lesion:** signs indicative of a brain lesion
  - **Pituitary Dysfunction:** signs of MPHD
  - **Congenital GHD:** neonatal symptoms and signs of GHD

MPHD=multiple pituitary hormone deficiency

Cohen P, et al. J Clin Endocrinol Metab. 2008;93(11):4210–4217.
Growth Hormone Research Society. *J Clin Endocrinol Metab*. 2000;85(11):3990–3993.

Screening and Diagnostic Testing for ISS

Medical History and Physical Evaluation	Laboratory Evaluation
Medical and family history	Complete blood count
Physical examination including • Phenotypic characteristics • Body proportions • Pubertal staging	TSH
	Free T_4
	IGF-1
Birth history • Abnormalities of fetal growth • Perinatal complications	Celiac disease screening
	Bone X-ray/skeletal survey
Maternal history during pregnancy • Past illnesses and/or chronic diseases • Medication use • Nutritional status	Karyotype • Boys with genital abnormalities • Girls with unexplained short stature

TSH=thyroid stimulating hormone
T_4=thyroxine

Cohen P, et al. *J Clin Endocrinol Metab*. 2008:93(11):4210–4217.

Small for Gestational Age: Definition

- Definition
  - SGA refers to the size of the infant at birth
  - Birth weight <2500 g at a gestational age of more than 37 weeks or a birth weight or length below the third percentile for gestational age
  - Includes neonates with either low birth weight, low birth length, or both low weight and length for gestational age
  - Children with SGA usually do not have GH or IGF-1 deficiencies
- Diagnosis is facilitated by
  - Accurate birth weight and length measurements
  - Ultrasonographic gestational dating performed during pregnancy

Lee PA, et al. *Pediatrics*. 2003;111(6 Pt 1):1253–1261.

Small for Gestational Age: Prognosis

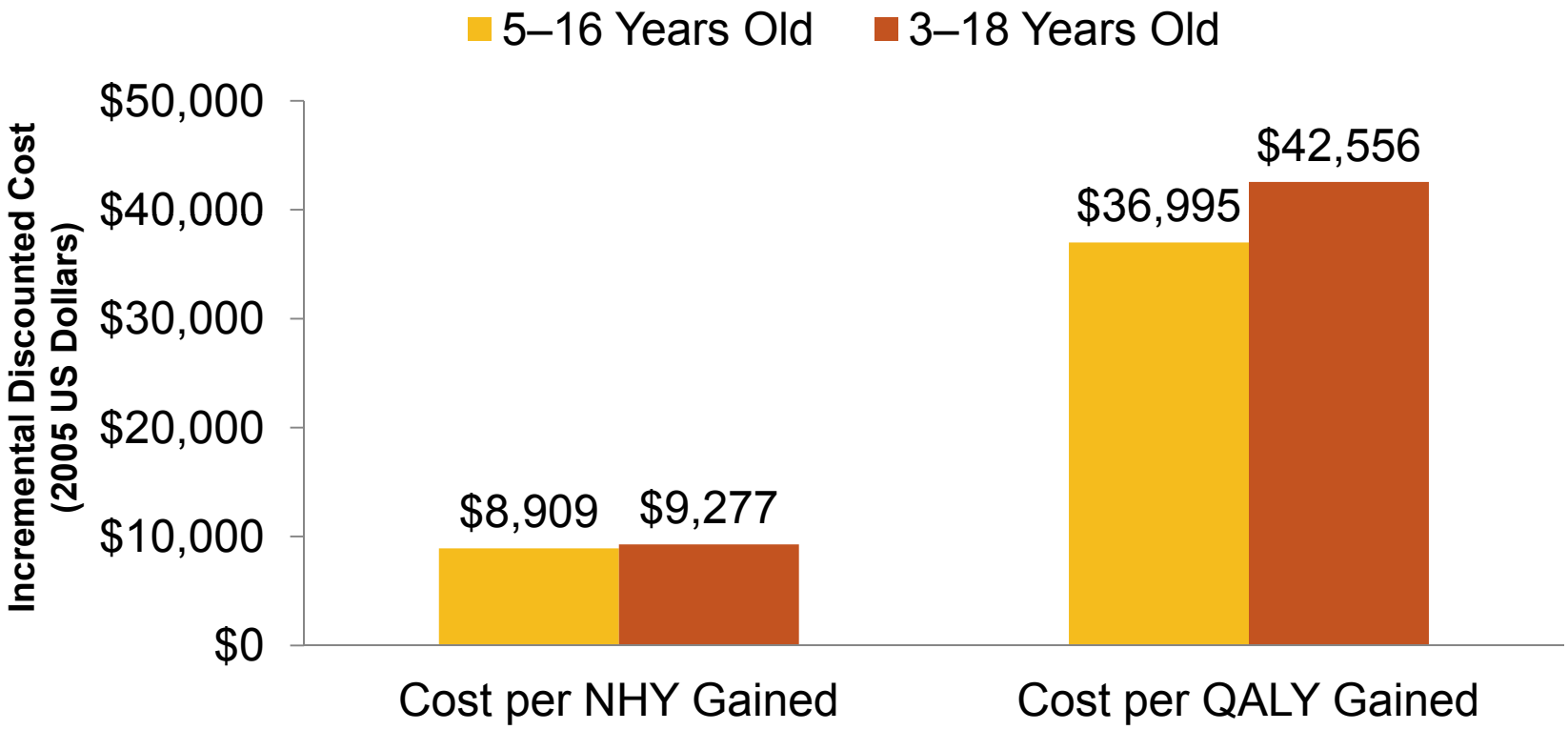
- Prognosis
  - Most children born SGA achieve catch-up growth during the first 6–12 months of life
  - If they have not caught up by 2 years, they are unlikely to do so in the future

Lee PA, et al. *Pediatrics*. 2003;111(6 Pt 1):1253–1261.

ICD-9 Codes Associated With a Diagnosis of Pediatric Growth Hormone Deficiency

ICD-9 Code	Primary Diagnosis
253.2	Panhypopituitarism
253.3	Growth hormone deficiency
585	Chronic renal insufficiency
759.81	Prader-Willi Syndrome
759.89	Noonan's Syndrome
758.6	Turner's Syndrome
764.00	Small for Gestational Age
783.43	Idiopathic Short Stature

GH Therapy Is Cost-effective in Children With GHD



Treatment of GHD (somatropin 0.030 mg/kg/day vs no treatment) was assessed using decision analytic modeling in two hypothetical cohorts of children: 1) 5 to 16 years, 2) 3 to 18 years.

NHY=normal height years
QALY=quality-adjusted life-years

Joshi AV, et al. *Curr Med Res Opin*. 2006;22(2):351–357.

ISS and SGA: Summary

- Children with ISS and SGA usually do not have GH or IGF-1 deficiencies, but GHD must be excluded to make the diagnosis
- Diagnosis of both ISS and SGA can be challenging due to the absence of clear laboratory indicators

Currently Available rhGH and Administration Devices

Approved Indications for Currently Available rhGH

Drug	Manufacturer	FDA-Approved Indications				
		GHD (Pediatric/Adult)	Turner syndrome	CRI	ISS	Other
Genotropin®[1]	Pfizer	X	X			PWS, SGA
Humatrope®[2]	Eli Lilly	X	X		X	SHOX
Norditropin®[3]	Novo Nordisk	X	X		X	Noonan Syndrome, SGA
Nutropin®[4]	Genentech	X	X	X	X	
Nutropin AQ®[5]	Genentech	X	X	X	X	
Omnitrope®[6]	Sandoz	X				
Saizen®[7]	EMD Serono	X				
Serostim®[8]	EMD Serono					HIV wasting or cachexia
Tev-Tropin®[9]	Gate/Teva	X (pediatric only)				
Zorbtive®[10]	EMD Serono					SBS

GHD=growth hormone deficiency
CRI=chronic renal insufficiency
ISS=idiopathic short stature
PWS=Prader-Willi syndrome
SGA=small for gestational age
SHOX=short stature homeobox genen
HIV=human immunodeficiency virus
SBS=short bowel syndrome

Drug Facts and Comparisons. 2009.

Examples of Currently Available rhGH Administration Devices

Growth Hormone	Device
Genotropin® (somatropin; rDNA origin)	Pen® 5 and Pen® 12, MiniQuick® premixed
Humatrope® (somatropin; rDNA origin)	HumatroPen® with cartridges, vial
Norditropin® (somatropin; rDNA origin)	NordiFlex®, FlexPro®, and NordiPen® with cartridges
Nutropin and AQ® (somatropin; rDNA origin)	Nutropin AQ Pen® with cartridges, AQ NuSpin™, vial
Omnitrope® (somatropin; rDNA origin)	Pen 5 and Pen 10, vial
Saizen® (somatropin; rDNA origin)	cool.click™ needle-free injector system, one.click® auto-injector pen, and easypod® needle injector system
Tev-Tropin® (somatropin; rDNA origin)	Tev-Tropin vial and needle-free T-Jet®
Valtropin® (somatropin; rDNA origin)	Valtropin syringe and needle

Preferred Features of an rhGH Administration Device

- Patient preferences for rhGH injection include
  - Reliability
  - Ease of use
  - Lack of pain during injection
  - Safety on use and in storage
  - Number of steps in preparation before, during, and after use

Dumas H, et al. *BMC Endocr Disord*. 2006;6:5.

Variables Impacting Long-term Adherence to GH Therapy

Variable	Frequency of Missed Injections			
	0 per Week	Up to 1 per Week	>1–2 per Week	>2 per Week
Age of patient	12.3	11.9	11.9	14.2
Duration of GH therapy (yrs)	1.6	1.8	2.8	4.4*
Patient allowed to use their preferred administration device (%)	81	68	58	23*
Short duration of GH Rx (<4 wks/Rx)	10	6	27	50*

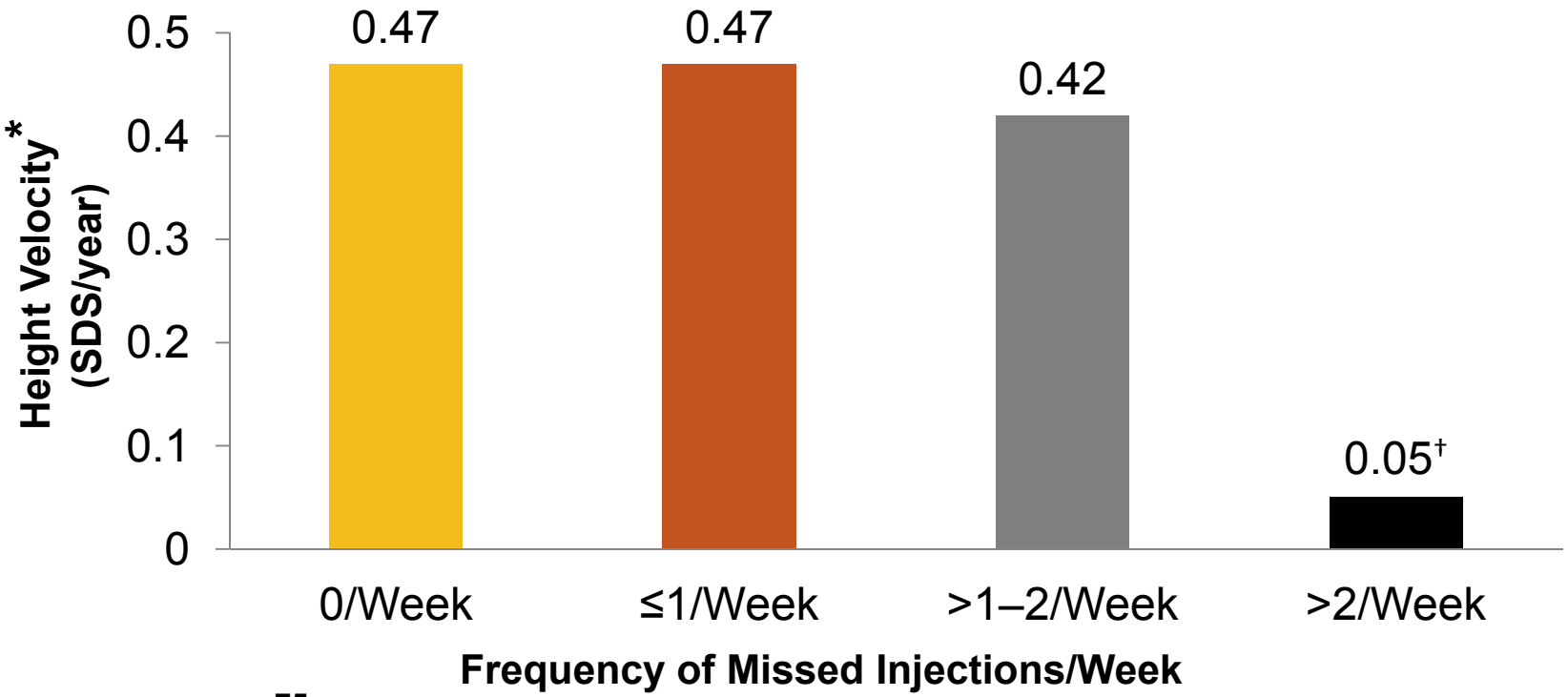
n=75
Mean age=12.3 years
Cross sectional data
Mean duration of GH treatment=1.9 years
GH dose=0.8 mg/kg/day

GH devices included automatic injection devices (n=38), manual injection pen devices (n=33), and needle-free injection devices (n=4).

*P<0.005

Kapoor RR, et al. *Arch Dis Child*. 2008;93(2):147–148.

Greater Number of Missed Injections Associated With Lower Growth Rate



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GH dose=0.8 mg/kg/day.

36% (27/75) missed 0 injections/week;
25% (19/75) missed ≤1/week;
16% (12/75) missed >1–2/week;
23% (17/75) missed >2 injections/week.

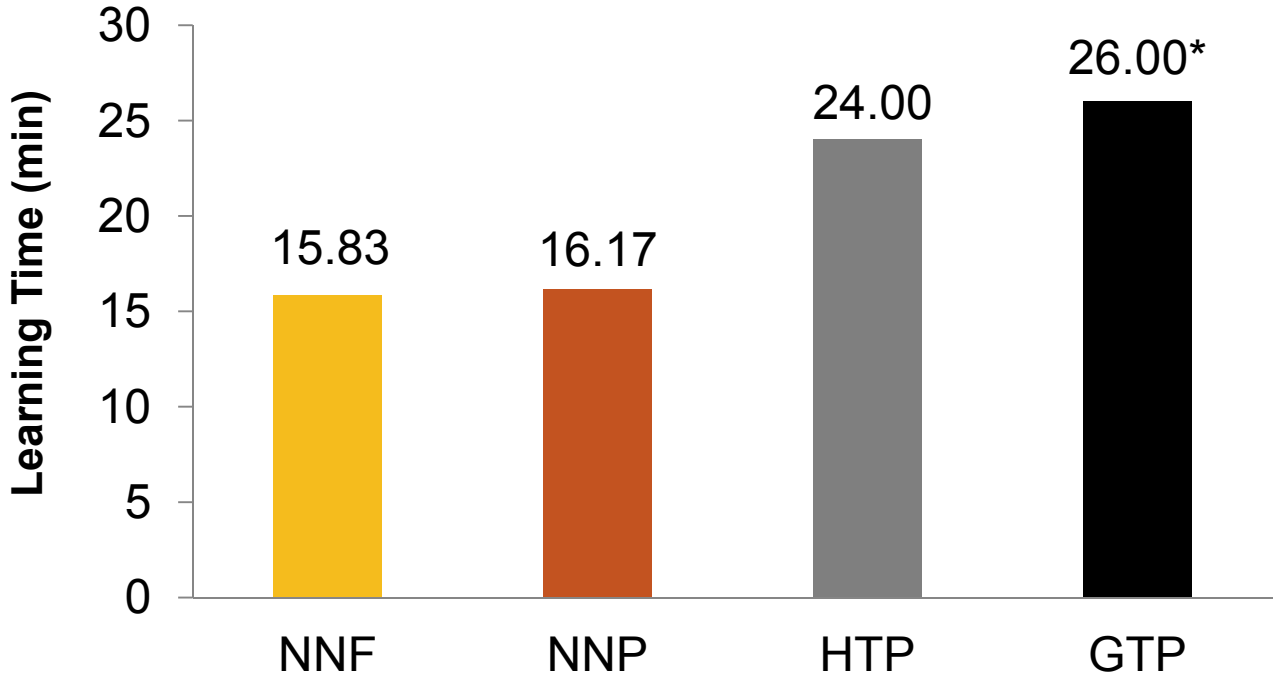
*Adjusted for age and duration of GH
†*P*<0.05therapy
Kapoor RR, et al. *Arch Dis Child*. 2008;93:147–148.

Ease of Use Can Impact Therapeutic Adherence

- rhGH often must be either parent-administered (in the case of small children) or self-administered, often for several years[1]
- Adherence to therapy can be negatively affected by the time required to prepare and administer the drug[1,2]
- Easier-to-use administration devices require less training[1,2]

1. Wickramasuriya BP, et al. *Horm Res*. 2006;65(1):18–22.
2. Dumas H, et al. *BMC Endocr Disord*. 2006;6:5.

Comparison of Time Required to Learn How to Use Common Administration Devices



NNF=Norditropin Nordiflex® 5 mg
NNP=Norditropin NordiPen® 5 mg

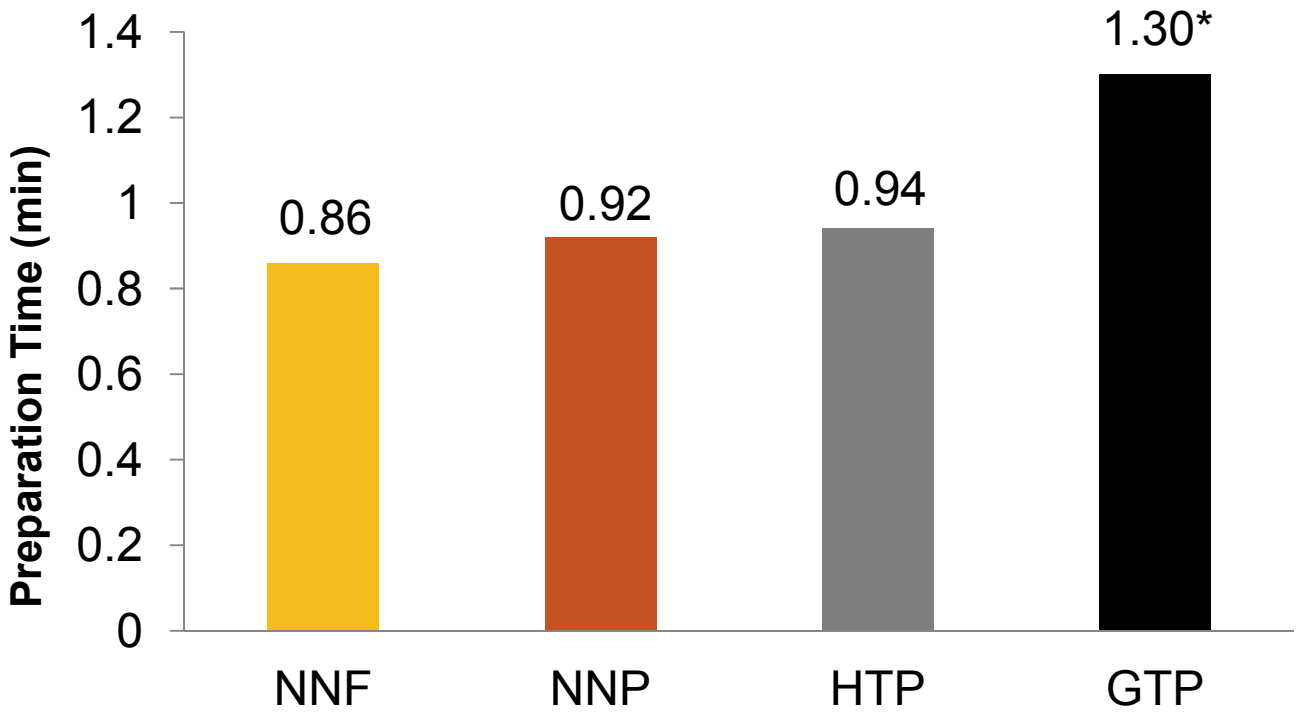
HPT=HumatroPen® 6 mg
GTP=Genotropin Pen® 5.8 mg

N=6 nurses; each nurse completed 5 simulations for the 4 pen devices resulting in a total number of 30 observations each device across 2 dosing simulations (ie, n=60 observations per pen device).

***P*<0.05 vs NNF**

Nickman NA, et al. *BMC Nurs*. 2010;9:6.

Comparison of Time Required to Prepare Common Devices to Deliver a Single Dose



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rhGH Administration: Summary

- Several devices are available to administer rhGH
  - Patients given a choice of device have greater adherence
- Ease of use, reliability, safety, and amount of preparation required all influence patient satisfaction with the administration device
- Patient satisfaction can influence adherence to GH therapy
- Higher adherence is associated with greater height velocity