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\(^1-3\)

AACE Medical Guidelines for Growth Hormone Use
AACE 2009: Background

- 2003 AACE guidelines identified the benefits of GH replacement in adults with GHD including:
  - 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

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

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)

**AACE 2009: Diagnosis of Adult GHD**

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**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 IGF-1
    - (≥0 SDS)
    - Observe
  - High suspicion
  - Multiple pituitary hormone deficiencies
    - Low IGF-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

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**Legend**

- Treat if peak GH ≤11.0 µg/L in patients with BMI <25 kg/m², peak GH ≤8.0 µg/L in patients with BMI ≥25 and <30 kg/m², or peak GH ≤4.0 µg/L in patients with BMI ≥30 kg/m²

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IGF-1=insulin-like growth factor 1
ITT=insulin tolerance test
GHRH=GH releasing hormone
ARG=arginine
AACE 2009: Diagnosis of Adult GHD

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

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ITT or GHRH/ARG

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ITT remains the gold-standard test for diagnosing adult GHD

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GHRH/ARG
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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\(^1\)

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.

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

• 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

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

• 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

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

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

# Screening and Diagnostic Testing for ISS

## Medical History and Physical Evaluation

<table>
<thead>
<tr>
<th>Medical and family history</th>
<th>Complete blood count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination including</td>
<td>TSH</td>
</tr>
<tr>
<td>• Phenotypic characteristics</td>
<td>Free T&lt;sub&gt;4&lt;/sub&gt;</td>
</tr>
<tr>
<td>• Body proportions</td>
<td>IGF-1</td>
</tr>
<tr>
<td>• Pubertal staging</td>
<td></td>
</tr>
<tr>
<td>Birth history</td>
<td>Celiac disease screening</td>
</tr>
<tr>
<td>• Abnormalities of fetal growth</td>
<td>Bone X-ray/skeletal survey</td>
</tr>
<tr>
<td>• Perinatal complications</td>
<td></td>
</tr>
<tr>
<td>Maternal history during pregnancy</td>
<td>Karyotype</td>
</tr>
<tr>
<td>• Past illnesses and/or chronic diseases</td>
<td>• Boys with genital abnormalities</td>
</tr>
<tr>
<td>• Medication use</td>
<td>• Girls with unexplained short stature</td>
</tr>
<tr>
<td>• Nutritional status</td>
<td></td>
</tr>
</tbody>
</table>

TSH=thyroid stimulating hormone  
T<sub>4</sub>=thyroxine

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

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

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

<table>
<thead>
<tr>
<th>ICD-9 Code</th>
<th>Primary Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>253.2</td>
<td>Panhypopituitarism</td>
</tr>
<tr>
<td>253.3</td>
<td>Growth hormone deficiency</td>
</tr>
<tr>
<td>585</td>
<td>Chronic renal insufficiency</td>
</tr>
<tr>
<td>759.81</td>
<td>Prader-Willi Syndrome</td>
</tr>
<tr>
<td>759.89</td>
<td>Noonan’s Syndrome</td>
</tr>
<tr>
<td>758.6</td>
<td>Turner’s Syndrome</td>
</tr>
<tr>
<td>764.00</td>
<td>Small for Gestational Age</td>
</tr>
<tr>
<td>783.43</td>
<td>Idiopathic Short Stature</td>
</tr>
</tbody>
</table>
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.

Cost per NHY Gained

- 5–16 Years Old: $8,909
- 3–18 Years Old: $9,277

Cost per QALY Gained

- 5–16 Years Old: $36,995
- 3–18 Years Old: $42,556

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

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

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

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  

### Examples of Currently Available rhGH Administration Devices

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

# Variables Impacting Long-term Adherence to GH Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency of Missed Injections</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 per Week</td>
</tr>
<tr>
<td>Age of patient</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.3</td>
</tr>
<tr>
<td>Duration of GH therapy (yrs)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.6</td>
</tr>
<tr>
<td>Patient allowed to use their preferred administration device (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>81</td>
</tr>
<tr>
<td>Short duration of GH Rx (&lt;4 wks/Rx)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
</tr>
</tbody>
</table>

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
Greater Number of Missed Injections Associated With Lower Growth Rate

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

n=75
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
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\(^1,2\)

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

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*P<0.05 vs NNF
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