Growth promoting treatment:
When discretion is the better part of value

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Disclosures

• I have no conflicts to report
• I have been conflicted about this topic for 30 years
• By the end of this lecture, I hope you feel conflicted too
Imminent challenge:
how to push back against the push back

Quartz Insurance Growth Hormone Coverage policy:
“Excluded: Medications, including Growth Hormone, used to treat growth retardation except when endogenous production of growth hormone is inadequate and clinical criteria are met. **Coverage is not extended for short stature syndrome or any other related growth abnormalities.**”
Key definitions and distinctions

• GH augmentation vs. GH replacement
  • Cost-conscious vs. cost-effective
  • Critical thinking vs. criticism
Toward cost-conscious hGH-for-height treatment

• Candidacy criteria
• Alternative treatment options
• Therapeutic objectives
• Minimizing risk
• Outcomes:
  – targeted usage
  – lowest effective dosage
  – reduced treatment duration

Allen DB. Horm Res Paediatr. 2017;87(3):145-152
How did we get here?
From hormonal replacement to enhancement

- Medical services deserved to treat disease and disability and not to enhance performance or appearance
- Role of medicine to make people normal competitors, not equal competitors
- **Expansive biotechnology** - treatments for disease are found by physicians and industry, to have benefits in other situations that do not fit clearly into the role of medicine
Growth hormone therapy for short stature: Panacea or Pandora’s box?

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- If hGH-for-height is effective -
  - GH responsiveness, not just GHD, a criterion for hGH treatment.
  - Stature-handicapped children considered for treatment.
  - No societal obligation to increase height > lower adult normal range
  - Objective: reduce burdens of severe short stature without endorsing "heightism"
- Letters to Editor Responses:
  - No way: GHD = treatment, non-GHD = enhancement
  - Not going to work: Ethics should wait until efficacy trials completed
Assumptions propelling hGH expansion

• Disability linked to short stature alleviated by hGH-induced height gain
• Pharmacological hGH is safe during and after treatment
• Interests of parents, prescribers, and industry should and would be supported by payers
Safety-sales linkage in the National Cooperative Growth Study:

- 34 PubMed NCGS articles about positive hGH treatment, 13 about safety
- Most in non-FDA-approved (at the time) conditions
- Opinion leaders influence prescribing
- Need for long-term post-treatment surveillance

Allen DB. J Clin Endocrinol Metab. 2010 Jan;95(1):52-5
Post-marketing investigation → expert opinion → accepted practice → sufficient market? → indication

- Childhood GHD
- Idiopathic/familial short stature
- Constitutional growth delay
- IUGR
- Turner syndrome
- Skeletal dysplasias
  - Hypochondroplasia, hypophosphatemia, etc.
- Noonan syndrome
- Prader-Willi syndrome
- Down syndrome
- Adult GH deficiency
- Catabolic states
  - Post-operative wound healing
  - Burns

Indications approved by the FDA

- Regenerative/repair states
  - Fractures
  - Peripheral nerve damage
- Neural tube defects
  - Spina bifida
  - Myelomeningocele
- Chronic illness
  - GC-dependent disorders
  - Chronic renal failure
  - Cystic fibrosis
  - AIDS wasting
  - Inflammatory bowel disease
- Aging
- Athletic healing/enhancement

Significant off-label prescribing
• FDA -> shortness from multiple diagnoses entitled to treatment
• Augmentation endocrinology sanctioned
• Concern -> vulnerability of open-endedness
  – Initiation entitlement: diagnostically “qualified” but nondisabled children
  – Therapeutic goal: maximum height vs. normal height

Growth Promotion Ethics and the Challenge to Resist Cosmetic Endocrinology

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Cost conscious candidacy
Focusing Illusion: when judgments about a characteristic derived from a subset are applied globally to all subjects with the characteristic.

Decision point A: hGH treatment initiation?

Evidence-based counseling:

• Child’s height is likely not the primary factor affecting psychological well-being (focused illusion)
• hGH -> modest height increase but will not predictably improve psychosocial well-being
• Benefit/risk/cost analysis uncertain for otherwise healthy child
• Default to non-treatment if child of assenting age dissents
Cost-conscious treatment choices
Fig. 1. Twin boys with persistent size discrepancy since birth present with short stature at the age of 3 years. Screening laboratory evaluation of the smaller twin is nonrevealing, and observation recommended. During kindergarten, concern about severe short stature and emotional well-being of the smaller twin prompts provocative testing (peak GH 8.5 ng/mL), MRI (normal), and (time A) institution of hGH. At time B, the hGH-treated twin is now taller than the untreated twin, prompting parental concerns of distress in the now shorter twin, and both are beginning puberty. At time C, the hGH-treated twin has reached a height in the lower-normal adult male range. Key questions for repeated informed assent discussions are posed for A–C.
Decision Point B: interrupt hGH to reassess need for and assent to continued treatment?

• Evidence: most IGHD patients have a normal GH test after puberty
• Standard practice: treat to epiphyseal closure or “satisfactory” height
• Alternative:
  – Trial off hGH for IGHD/ISS children at puberty followed by observation and re-testing if needed
  – Obtain adolescent informed assent to ongoing hGH treatment
  – Minimize use of hGH making children destined for normal stature taller than others
Short Stature in Childhood — Challenges and Choices

David B. Allen, M.D., and Leona Cuttler, M.D.

Approximate Projections of the Growth Trajectory and Adult Height Associated with Various Treatments for Short Stature
# Treatment of SS: benefits and burdens

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Estimated Adult Height in Inches (±1.3 in.)</th>
<th>Psychological Benefit or Harm</th>
<th>Estimated Treatment Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>No medication</td>
<td>65</td>
<td>Uncertain</td>
<td>No cost for drug with or without cost for counseling</td>
</tr>
<tr>
<td>Low-dose androgen (i.e., oxandrolone)</td>
<td>65</td>
<td>Uncertain</td>
<td>Oxandrolone, 2.5 mg/day, $2,920/yr × 2.5 yr = $7,300</td>
</tr>
<tr>
<td>Human growth hormone until onset of puberty</td>
<td>66</td>
<td>Uncertain</td>
<td>Human growth hormone at dose for idiopathic short stature (0.375 mg/kg/wk) × 2.5 yr = $76,050</td>
</tr>
<tr>
<td>Human growth hormone until normal range (e.g., 5th percentile) of adult height</td>
<td>66</td>
<td>Uncertain</td>
<td>Human growth hormone × 4 yr = $133,087</td>
</tr>
<tr>
<td>Human growth hormone until completion of growth</td>
<td>66–67</td>
<td>Uncertain</td>
<td>Human growth hormone × 5 yr = $176,962</td>
</tr>
<tr>
<td>Human growth hormone until maximum attainable height</td>
<td>68</td>
<td>Uncertain</td>
<td>Human growth hormone at dose for idiopathic short stature × 2.5 yr plus “pubertal” dose of human growth hormone (0.7 mg/kg/wk) × 2.5 yr = $264,420</td>
</tr>
</tbody>
</table>

*To convert the values for inches to centimeters, multiply by 2.54. Costs of therapy were based on estimates of weight derived from the 3rd percentile for age: a mean of 28 kg from 11 up to 13 years of age, 36 kg from 13 up to 15 years, and 45 kg from 15 to 16 years. Medication costs, obtained from Epocrates Online, were $50 per milligram of human growth hormone (the lowest current available per-milligram cost listed was $50 to $75 per milligram) and $8 per 2.5-mg tablet of oxandrolone.

Cost-conscious therapeutic objectives
How tall is tall enough?

Fig. 1. Twin boys with persistent size discrepancy since birth present with short stature at the age of 3 years. Screening laboratory evaluation of the smaller twin is nonrevealing, and observation recommended. During kindergarten, concern about severe short stature and emotional well-being of the smaller twin prompts provocative testing (peak GH 8.5 ng/mL), MRI (normal), and (time A) institution of hGH. At time B, the hGH-treated twin is now taller than the untreated twin, prompting parental concerns of distress in the now shorter twin, and both are beginning puberty. At time C, the hGH-treated twin has reached a height in the lower-normal adult male range. Key questions for repeated informed consent discussions are posed for A–C.
Therapeutic objective: maximal height or normal height?

- Adult QOL is normal in short people and not predictably improved by hGH-mediated height gain
- Thus, endpoints cannot be differentiated by QOL outcomes
- Last 1–3% of height gain increases expenditure by ~20%
- No coherent entitlement to communal resources to be made taller than other short normal people
- Proper therapeutic goal: normal opportunity range
- Families can use personal resources for additional treatment

Cost-conscious risk avoidance
“Does the FDA really believe that a height increase is worth an increased risk of death, or worth any risk to a healthy child, when it has never been shown to have any actual medical benefit?”
Morbidity and mortality post-hGH treatment

• Confounder: disorders treated with hGH have higher morbidity and mortality risk
• Aggregate evidence does not support association between hGH exposure and all-cause mortality
• Any potential risk may be related to dosage
• Counseling about ongoing studies of long-term safety advised

Steps to minimize potential hGH risk

• Aiming for lowest effective hGH dose and duration
  – low dose initiation
  – growth rate-based titration
  – IGF-1 monitoring?
  – Interrupt ± discontinue hGH treatment?
  – Informed assent emphasizing evidence-based approach to growth concerns
Reconciling evidence, value, and resource allocation

- IOM: value (outcome quality/cost) should guide health care redesign
- Evidence-based decisions should guide innovations (GRADE approach)
- Critical benefit assessment should be balanced with potential risk

Best defense is good offense: asserting the value of cost-conscious hGH treatment

- Height-promotion prescribing practices that:
  - Recommend non-treatment for most short children
  - Initiate hGH treatment only after evidence-based informed assent
  - Utilize alternative less costly options when possible
  - Take steps to minimize hGH treatment duration and dosage
  - Objective: lessen disability of extreme short stature while resisting enhancement of normal adult stature.

Thank you this award and for the opportunity to present