

## Clinician and Payer Issues in Managing Growth Hormone Deficiency

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### **Abstract**

Growth hormone (GH) therapy has an established record of efficacy in the treatment of children with proven GH deficiency. It has also shown benefit, including nongrowth-related benefit, in other nontraditional pediatric uses, but managed care plans hesitate to reimburse clinicians for such uses. In adults and in those individuals who are in transition from GH-deficient children to adults, GH deficiency is sometimes difficult to diagnose. In such cases, growth rate cannot be used to guide therapy and the outcomes measures are either "softer" (eg, quality of life) or very long term (eg, bone mineral density changes). Also, there are no long-term data to show GH treatment in adults affects the cardiovascular-associated morbidity and mortality from GH deficiency. However, several cardiovascular risk factors, such as hypercholesterolemia and abdominal adiposity, improve in GH-deficient adults who receive GH treatment. Clinicians and payers often appear at odds with each other over their primary goals for managing the various forms of GH deficiency. However, upon closer examination, both parties do share common treatment goals and strive to do the right clinical thing. Identifying the cost of treatment emphasizes the need for evidence-based medicine.

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Managed care is now the predominant form of healthcare in the United States. It has undergone rapid growth in the past decade and, along with healthcare providers, employers, and members, has experienced the growing pains that accompany fast-paced change.

Reimbursement policies have often been a source of dispute between payers and clinicians, particularly concerning diseases and new technologies that do not have a clearly defined diagnostic algorithm or approved use. In particular, new technologies are one of the most influential cost drivers in the healthcare industry today, perhaps responsible for as much as 50% of medical cost increases. With the rapid development of new technologies, including drugs, devices, and treatments, managed care plans have developed strategies for evaluating new technology, and chief among these strategies is evidence-based review.

It is no longer considered acceptable for managed care plans to evaluate new technology after it has been introduced. Determining the relative value of a new technology and drafting coverage policies must take place through evaluation of safety, efficacy, and cost data and must take place quickly. Managed care plans also need a process to review and update coverage policies on a regular basis. The ultimate goal is to spend healthcare dollars wisely, so they are not wasted

on less than optimal treatment, and effective treatment is not withheld from those who can truly benefit.

Clinicians and payers must face many of the challenges described above with regard to growth hormone (GH) therapy. Several diseases are treatable with GH replacement, and their diagnosis is clearly defined. However, questions arise regarding more ambiguous clinical situations (eg, borderline GH-deficient patients), resulting in inconsistent reimbursement policies across managed care plans and a lack of understanding between clinicians and payers of the key clinical and insurance issues. This review briefly addresses the history of GH therapy, analyzes its current use in pediatric, nontraditional pediatric, adult, and transitional patients, and examines the associated managed care issues.

### **Gaining Perspective on the Role of GH**

*GH Uses.* GH is administered to correct a complete or partial GH deficiency in adults and children. The primary action of GH is to promote linear growth. GH has numerous other physiological effects, which are reflected in the differing treatment goals for children and adults.

*The History of GH.* GH therapy has been available for 40 years. For the first 25 years, GH was available in limited quantities because it was isolated directly from cadaver pituitaries. As a result, GH was administered only to children who were very short, grew at a very slow rate, and were extremely GH deficient with minimal or no response on a provocative test for GH. Supply was also the key determinant for dosage and duration of treatment. With the availability of recombinant GH, questions regarding eligibility for treatment, dosing, duration, and the definition of GH deficiency were all open for exploration.

GH deficiency is difficult to diagnose in some cases. Approximately 70% of pediatric patients are classified as idiopathic, and many of them have no notable physi-

cal features. In adults, GH deficiency is difficult to diagnose because there is no growth rate to measure and the therapeutic benefits of GH are more broadly defined for adults than for children. Before diagnosing an adult or child as GH deficient, other medical conditions that may cause growth failure must be ruled out.

Traditionally to determine GH deficiency in children, emphasis has been placed on measuring serum, insulin-like growth factor 1 (IGF-1), or IGF-binding protein 3 (IGFBP-3) levels; or measuring the serum GH response to any of several stimuli (provocative testing), the most reproducible of which is insulin-induced hypoglycemia. Other measures are the growth rate and overall growth pattern of the child. In addition, the likelihood of GH deficiency in a patient with hypothalamic or pituitary disease increases with the number of pituitary trophic hormones that are missing. A patient who lacks gonadotropins, adrenocorticotrophic hormone, and thyroid-stimulating hormone is very likely to be GH deficient.

GH testing has many limitations, including inpatient and age variations, poor standardization of assays across laboratories, conflicting serum responses to provocative tests, conflicting results between growth data and provocative tests, and no readily identifiable bimodal distribution in GH secretion or response to provocative stimuli between normal children and those with GH deficiency.

Unfortunately, because of the lack of research into alternative criteria for diagnosis, managed care plans rely on GH testing for an objective measure of the disease. This is one source of dispute between the clinical and managed care communities.

### **Use of GH in the Pediatric Population**

*Diagnostic Issues.* Diagnosis is one of the greatest clinical challenges of managing GH deficiency in children. It requires a multifaceted approach that includes clinical and auxologic assessment, biochemical testing of GH levels, provocative testing, and radiologic evaluation. Each component is necessary for the clinician

to make a diagnosis, and each is a separate billing event requiring payer approval. The establishment of guidelines can help physicians and payers form a more standardized approach. Recently developed consensus treatment guidelines titled, Diagnosis and Treatment of GH Deficiency in Childhood and Adolescence, will be published soon. Guidelines on the use of GH in all children with short stature already have been published by the Lawson Wilkins Pediatric Endocrine Society.<sup>1</sup>

A short child is defined as one whose height is 2 standard deviations (SDs) or more below the mean for that age. Evaluation of GH deficiency should not be initiated in short children until other possible causes of growth failure can be excluded (eg, hypothyroidism, chronic systemic diseases, Turner syndrome [TS], or skeletal disorders).

The initial biochemical assessment involves measuring serum IGF-1 and IGFBP-3. Values below 2 SDs of the mean for that age are strongly indicative of GH deficiency; values below 1 SD should be followed by GH testing. One of the difficulties in assessing GH secretion is that it is normally secreted in a pulsatile manner. For example, a normal individual may have low levels during waking hours with several secretion spikes during sleep. Also, there are wide variations in the degree of GH deficiency and in the patient's response to GH stimuli (ie, normal or near-normal levels of GH but poor response to the stimuli). In fact, GH provocative testing does not correlate well with GH secretion, as shown in a study comparing patients with GH deficiency, GH neurosecretory dysfunction, idiopathic short stature (ISS), or normal stature.<sup>2</sup> Many children diagnosed with idiopathic GH deficiency are considered borderline cases. Historically, the minimum level of GH secretion has been 10 ng/mL after provocation, but this value can be considered arbitrary.

Provocative testing is an often imprecise indicator of GH deficiency. It is also expensive and uncomfortable for the patient. Results frequently do not distinguish partial GH deficiency from ISS. In fact, the different manifestations of GH deficiency may be a continuum rather than discrete disease states. Although the insulin-induced hypoglycemia test is the most reproducible provocative test, it requires close medical supervision; in several centers, it has been replaced by other tests, such as arpinine, oral levodopa (L-dopa), clonidine, GH-releasing hormone, or a combination of these tests.

Direct measurement of IGF-1 and IGFBP-3 also presents a conundrum because there are children with low GH levels who fail provocative testing but have normal IGF-1 levels and vice versa. Similar results are found with IGFBP-3. In fact, GH testing and IGF-1/IGFBP-3 results for such children are sometimes not reconcilable.<sup>3</sup> These patients may not have classic GH deficiency but an abnormality of the GH-IGF axis. Given the complexity of the endocrine system, it is expected that the controlling factors in growth are not limited to a few hormones and that diagnosis cannot be reduced to 1 or 2 tests. Instead, diagnosis requires both biochemical analysis and clinical savvy. Clinicians must be prepared to integrate clinical and laboratory data: auxology (ie, growth rate and family history of height) and provocative GH testing or careful determination of the IGF system. Although this may result in overdiagnosis and overtreatment, it may be preferable to withholding treatment from those who would benefit. Insurers may need to refine their definition of GH deficiency and develop criteria that rely on the endocrinologist to appropriately evaluate clinical and biochemical data.

*Efficacy of GH Therapy in GH-Deficient Children.* GH has shown significant positive results in accelerating linear growth in GH-deficient

children, especially during the first 2 years of treatment (Figure 1).<sup>4,5</sup> GH has also been approved for non-growth-related uses in adults and children because of its important effects on fat, muscle, and bone development. GH restricts the differentiation of immature adipocytes into

mature adipocytes, improves lipid profiles, decreases visceral and truncal body fat, and improves bone density. GH treatment also dramatically improves quality-of-life parameters.

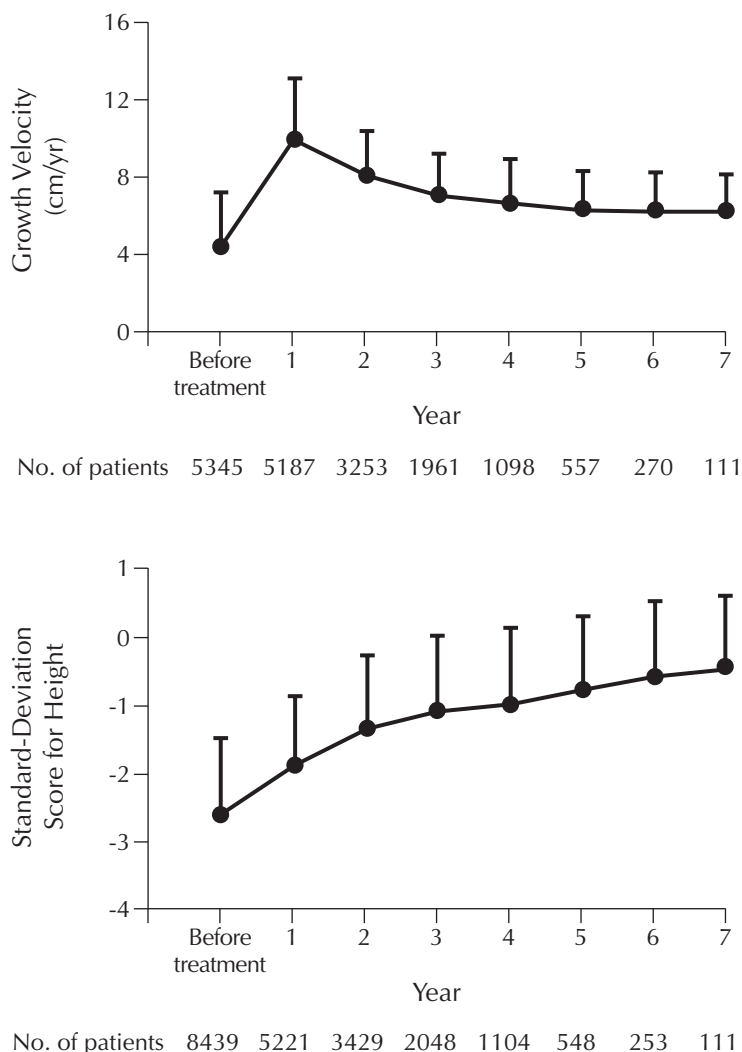
Some studies have shown that GH treatment in children results in significant improvement in all the above parameters, including total cholesterol, high density lipoprotein cholesterol, bone mineral density, lean tissue mass, and fat mass, and that such improvements reverse after discontinuation of treatment.<sup>6,7</sup> All of these outcomes are especially important in coverage considerations because in children with new-onset GH deficiency, height may still be normal yet the children display other physiologic abnormalities of GH deficiency.

*Nongrowth-Related Benefits of GH in Children With Prader-Willi Syndrome.* Nongrowth-related outcomes are also important in children with Prader-Willi syndrome (PWS). These patients have abnormal hypothalamic function, resulting in hypotonia and body composition changes characteristic of GH deficiency. Studies of children with PWS show that GH treatment significantly decreases body fat percentage and improves respiratory muscle function, physical strength, and agility. Only resting energy expenditure did not change.<sup>8,9</sup> As a result, quality of life for children with PWS improves dramatically because the children can more easily physically participate in normal activities for their age. It is difficult to test GH axes in children with PWS because their obesity suppresses GH production. Thus, the question of eligibility is not clearly answered.

**Coverage of Pediatric Treatment: Clinician Issues**

Clinicians suggest that responsiveness to GH treatment and not the diagnosis of GH deficiency should determine eligibility for borderline cases.<sup>10</sup> If this is the case, outcomes

**Figure 1.** Effect of GH on GH-Deficient Children



Source: Vance ML, Mauras N. Growth hormone therapy in adults and children. *N Engl J Med* 1999;341:1206-1216. Reprinted with permission from Massachusetts Medical Society. Copyright 1999. All rights reserved.

should include functional improvement and quality-of-life measurements, not just growth velocity. If functional improvement were to become the “gold standard” for successful therapy, payers may argue that this could lead to overtreatment. Payers should note however that if borderline cases on GH therapy fail to show functional improvement after an agreed-upon time frame, treatment would be terminated because no such improvements will occur. Thus, the issues of overtreatment and coverage become moot.

**Coverage of Pediatric Treatment: Payer Issues**

Every healthcare plan has its own review process, but all rely heavily on evidence-based medicine to formulate coverage policies. Healthcare plans turn to professional organizations and societies for recommendations on the usage of a new technology. They turn to outside professional consultants in an effort to make the best decisions regarding coverage and patient well-being. However, in ill-defined clinical situations (eg, lack of bimodal distribution among the patient population or no gold standard for diagnosis), it is becoming clear that flexibility of coverage policies is essential for the success of the managed care industry. As a result, healthcare plans often depend on the expertise of the clinician who sees the patient to assist them in determining coverage eligibility.

*Determining GH Eligibility.* Although clinicians and payers may dispute their respective goals with regard to approving GH treatment for a patient, they ultimately have similar processes. Both need the same information to make a decision, and the data must be as complete as possible. To determine whether a patient warrants GH treatment, a clinician will make a growth chart, look at key laboratory data, evaluate other parameters (such

as parental height), and eliminate other possible causes. He or she will make a decision to treat only after all of the appropriate information has been collected. Reviewers need the same quantity and quality of data to make a judgment of coverage.

Dosage, frequency, timing, and duration are critical variables in determining eligibility for coverage. Many companies usually start by approving coverage of an initial low dose or low frequency of doses and cover upward titration as necessary. Most healthcare plans will cover GH treatment for classical GH deficiency, as outlined in the published minimal criteria for treatment by the Lawson Wilkins Pediatric Endocrine Society (Table 1).<sup>1</sup>

**Nontraditional Pediatric Uses of GH**

The 3 nongrowth-related pediatric disorders treated with GH are TS, chronic renal insufficiency (CRI), and ISS.

*Turner Syndrome.* TS is a disorder of gonadal differentiation with many possible manifestations. However, short stature is the only phenotypic abnormality present in virtually all TS patients. Subnormal growth begins very early—in infancy and early childhood—so early identification and treatment are essential.<sup>11</sup>

Long-term GH treatment for TS is recommended and is effective only at pharmacologic doses (ie, 25% higher than conventional doses). Studies have shown that target heights are more likely to be reached with longer treatment periods (eg, 7 years).<sup>12-14</sup> The addition of oxandrolone, an androgen used to treat hypogonadism, to GH therapy has an additive effect on achieving target height<sup>12</sup> and should be considered if the height deficit is still significant by age 10 or 12 years. However, increases in growth rate with GH in patients with TS are not as sustained as they are in

those with GH deficiency. The average increase in final height for TS in GH-tested versus nonGH-tested girls can be as high as 12 to 15 cm.<sup>15</sup>

Although most payers will cover GH for TS—with the exception of those that specifically exempt biological agents in their coverage policies—disagreements between clinician and payer can occur regarding duration. Other sources of disagreement include initiation of GH treatment for older TS patients (For this population, some clinicians may wish to explore administering higher doses) and the issue of nongrowth-related benefits of GH therapy, which include improving lipid profiles and reducing body fat. It is assumed that the morbidity and mortality from cardiovascular disease would improve over the lifetime of the TS patient who receives long-term treatment (eg, 7 years). However, until long-term data examining this question

are available, payers are reluctant to accept that argument for long-term GH treatment.

**Chronic Renal Failure.** Chronic renal failure is the end stage of CRI, an irreversible decline in renal function caused by numerous pathologic processes. Chronic renal failure is present in more than 3000 children in the United States, but other estimates indicate it may be present in 4000 to 4500 US children.<sup>16</sup> The prevalence of CRI is by definition much higher.

CRI is most strongly characterized by growth failure in children (ie, mean adult height 2 SDs below the mean). Thus, individuals with CRI respond well to GH treatment. In a long-term study of 20 growth-retarded prepubertal children with CRI, mean standardized height improved from  $-2.6 \pm 0.8$  at baseline to  $-0.7 \pm 0.9$  at year 5 ( $P < 0.00005$ ). The maximum improvement in standardized height occurred in the first year, but continued sustained improvement was observed during the following 4 years of the study.<sup>17</sup> No advance in bone age was observed.<sup>17</sup>

GH is safe in children after renal transplantation and is approved by the Food and Drug Administration (FDA) for use in children with CRI prior to kidney transplantation. Early studies suggested that GH treatment may increase organ rejection or worsening of kidney function, but the most recent studies show no significant difference between treated and control groups in patient survival, graft survival, incidence of acute rejection episode, or time to first rejection episode.<sup>18,19</sup>

Despite positive clinical results and FDA approval, many questions surround the decision to approve coverage of GH in treating CRI patients. Patients experience a return to normal growth rate with kidney transplantation, but they are unlikely to experience catch-up growth. Therefore, the treatment goals are different from

**Table 1.** Minimal Criteria for Treatment with GH: Recommendations from the Lawson Wilkins Pediatric Endocrine Society Drug and Therapeutics Committee

<ul style="list-style-type: none"> <li>■ Determine that bone age-specific growth rate is less than the 25th percentile and represents an appropriately delayed bone age.</li> <li>■ Rule out conditions that suppress GH secretion (hypothyroidism, chronic nonendocrine disease, or psychosocial deprivation).</li> <li>■ Observe for a sufficient time to accurately determine growth rate.</li> <li>■ In girls, perform karyotype analysis to exclude Turner syndrome.             <ul style="list-style-type: none"> <li>• Offer children who fulfill the minimal criteria a trial of GH therapy.</li> <li>• Base decision to continue treatment on an adequate clinical response.</li> </ul> </li> </ul>
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Source: Reference 1.  
GH = Growth hormone.

other nontraditional pediatric disorders such as TS. Some plans may still require provocative tests, while others require statements of necessity each month from the physician. Overall, GH treatment for CRI is covered unless a plan does not cover biological agents or an employer chooses not to include GH in their benefits package (eg, self-funded employer groups, Employee Retirement Income Security Act [ERISA], and ERISA groups).

**Idiopathic Short Stature.** Like TS and GH deficiency, the diagnostic algorithm is not always clear for ISS. Patients with ISS are apparently “normal” children with height for age at or below the 5th percentile and normal GH responses to provocative stimuli. Such children often exhibit height 2.5 SDs below the mean. Diagnosis is primarily through exclusion of systemic disease, malnutrition, hypothyroidism, and classic GH deficiency.

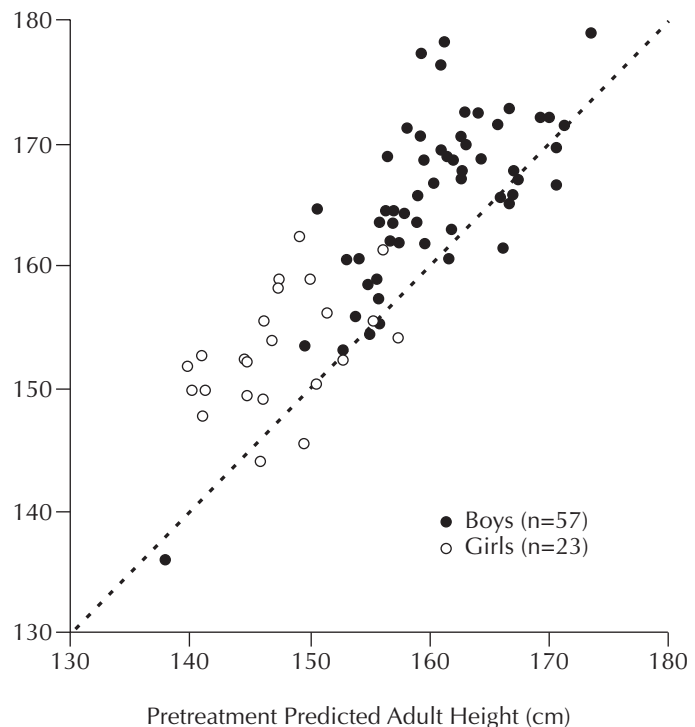
Several large clinical studies have shown the beneficial effects of long-term GH treatment for ISS, although the extent of the benefit varies between studies.<sup>20</sup> One reason may be the difference in target height definition between studies. The most recent study from the Genentech Collaborative Group showed that long-term GH treatment in children with ISS increased adult height to a level above the predicted value and above the adult height of untreated control children. However, wide individual variation in response to treatment was observed, and the study was not placebo controlled (Figure 2).<sup>21</sup>

**Coverage of Nontraditional Pediatric Treatment: Clinician and Payer Issues**

One of the greatest challenges regarding nontraditional pediatric uses of GH is predicting response to treatment. Results of GH treatment for ISS are promising; however, because of the borderline nature of the height change, payers are reluc-

tant to cover this indication. One measurable outcome is the improvement in quality of life among patients on long-term follow up. However, these patients may sometimes have unrealistic expectations of final height and thus become disappointed with the final result of GH therapy. Such expectations are reinforced by the sense of “heightism” in the United States (ie, discrimination based on height; being short is stigmatized).<sup>10</sup> Also, the diagnosis of ISS is not straightforward because of the lack of bimodal distribution, making

**Figure 2.** Final Versus Predicted Adult Height in Children With ISS: Effect of GH Treatment



Source: Hintz RL, Attie KM, Baptista J, Roche A. Effect of growth hormone treatment on adult height of children with idiopathic short stature. The Genentech Collaborative Group. *N Engl J Med* 1999;340:502-507. Reprinted with permission from Massachusetts Medical Society. Copyright 1999. All rights reserved. ISS = Idiopathic short stature; GH = growth hormone.

it difficult to identify this group of patients.

As with other pediatric indications, clinicians need to integrate all information to make an educated projection as to whether the patient with ISS will benefit from GH treatment. Although the studies have shown clear clinical benefit, the final decision to treat may be an individual judgment call, especially when

coverage is taken into consideration. Many payers rely on the experience and expertise of the clinician for individual cases, but they must always consider fairness—if one PWS patient is given treatment, for example, should it be given to every PWS patient?

Another dilemma is the extent to which payers should rely on FDA approval or other authority recommendations. Medical science changes rapidly, yet FDA review—although necessary to ensure product safety—remains slow. Payers may be open to covering treatments that are not yet FDA approved, but a mechanism to quickly update coverage policies based on new developments is necessary.

**Table 2.** Proposed and Approved Uses of GH in Adults

<ul style="list-style-type: none"> <li>■ GH deficiency                             <ul style="list-style-type: none"> <li>• Childhood-onset GH deficiency*</li> <li>• Adult-onset GH deficiency*</li> </ul> </li> <li>■ Aging—"somatopause"</li> <li>■ Catabolic states                             <ul style="list-style-type: none"> <li>• Respiratory failure</li> <li>• Burns</li> <li>• Acquired immune deficiency syndrome-related wasting*</li> </ul> </li> <li>■ Cardiomyopathy</li> </ul>
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GH = Growth hormone; \* = FDA approved uses.

### GH Treatment for Adults

There are several proposed and approved uses of GH in adults (Table 2) and several etiologies (Table 3). It is important to distinguish between them. Fewer than 10% of adults with GH deficiency had childhood-onset GH deficiency; 90% have a history of some other pituitary disease (eg, adenoma as a consequence of surgery or radiation therapy for pituitary adenoma).<sup>22</sup> As long-term studies on the effect of GH treatment on GH-deficient adults are not yet available, it is recommended that only patients with severe GH deficiency (ie, peak GH < 3 ng/mL after pharmacological stimulation) be treated. As patients become more educated and demand treatment, GH abuse may become more common in certain sectors of society.

**Table 3.** Etiology of Adult GH Deficiency

<ul style="list-style-type: none"> <li>■ Pituitary disease                             <ul style="list-style-type: none"> <li>• Tumor</li> <li>• Postirradiation</li> <li>• Postsurgery</li> <li>• Apoplexy</li> </ul> </li> <li>■ Hypothalamic disease</li> <li>■ Craniopharyngioma</li> <li>■ Posttrauma</li> <li>■ Postinfection</li> <li>■ Childhood-onset GH deficiency</li> </ul>
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GH = Growth hormone.

*Abuse Potential for GH.* With the emergence of scientific data indicating that GH secretion decreases progressively with age and that with the age-related decrease in GH secretion there is a resultant decrease in serum IGF-1, it can be speculated that the reduction in GH secretion with aging is responsible for abnormal cellular composition associated with aging.



This speculation has led to claims that GH is an effective antiaging compound. Internet sites abound with claims that GH can affect the following changes:

- Muscle mass increase without exercise
- Decrease in body fat composition
- Enhanced sexual performance
- Increased cardiac output
- Increased kidney function
- Faster wound healing
- Hair regrowth
- Mood elevation

None of these claims can be substantiated and long-term effects on muscle mass and function in the elderly do not seem beneficial enough to justify widespread hormone replacement therapy.<sup>23</sup>

GH is also being touted as useful to enhance athletic performance through its effect on muscle tissue. GH modestly increases nitrogen retention in most normal adults but only for a short period of time. It is therefore doubtful that the nitrogen retention associated with daily GH treatment results in an increase in contractile protein, improved muscle function, strength, or athletic performance.<sup>24</sup>

Managed care organizations need to be aware of such inappropriate uses of the drug and have plans to assure that approval of GH is for scientifically valid indications for their members.

*Diagnosis of GH.* Who should be tested for GH deficiency? Should patient complaints of fatigue and weight gain—2 very common characteristics of getting older—raise suspicion of GH deficiency? Guidelines on diagnosis and testing for adult GH deficiency were published in 1998 by the Growth Hormone Research Society.<sup>26</sup> Presently, testing for GH deficiency should be conducted only on patients with known hypothalamic pituitary disease in whom the pretest probability of being GH deficient is

high. Still, diagnosing adults with GH deficiency is difficult because 1) adults do not suffer from short stature unless they had GH deficiency as children and were not treated, 2) growth rates are not changing at this point, and 3) the patient's bone age is no longer a consideration. Up to 50% of children with isolated GH deficiency (IGHD) have a normal response to GH secretory stimuli when tested in adulthood.

As with childhood GH deficiency, there is no absolute diagnostic gold standard. Provocation tests give varied results, even in those without GH deficiency; IGF-1/IGFBP-3 levels are also poor indicators for adults particularly in those older than 50 years of age.<sup>25,26</sup> The insulin tolerance test or insulin-induced hypoglycemia is currently considered the gold standard, but it is difficult for the patient and requires close medical supervision.<sup>5,26</sup>

GH-deficient adults suffer the same nongrowth-related morbidity as GH-deficient children (ie, increased fat mass, decreased lean mass, decreased skeletal muscle strength and bone mineral density, abnormal lipids, and lower quality of life). As with children, excess fat tends to be visceral, which poses a higher risk for insulin resistance and cardiovascular disease, especially in women.<sup>27</sup> Numerous studies support the theory that GH deficiency severely affects the cardiovascular system, including cardiac structure and function (eg, decreased cardiac muscle thickness and left ventricular ejection fraction, diastolic dysfunction, and endothelial dysfunction).<sup>28-30</sup> Thus, the treatment goals for adults are not limited to immediate symptoms. Preventing the risk of future cardiovascular disease may be the most important reason for treating adults.

GH-deficient adults experience significantly lower quality of life because of decreased energy and mobility, disturbed sexual function, emotional lability, and feelings of social isola-

tion.<sup>31-33</sup> The degree of quality-of-life impairment varies among patients, and differences have been observed between those with childhood-onset versus adult-onset GH deficiency.

Perhaps as a result of improved quality-of-life parameters because of GH treatment, there is a very low dropout rate for adults on GH therapy, which is surprising for an injectable drug.<sup>32,34,35</sup> It is important to remember that all of the studies on GH treatment in adults apply only to proven GH-deficient patients and that treatment of nonGH-deficient patients with GH is not considered the current standard of care (eg, treatment of healthy elderly patients).

*Dosages in Adults.* Effective doses are lower in adults, with higher doses resulting in side effects (eg, fluid retention, muscle and joint pain, headache, or blurred vision). If hormone replacement therapy is meant to mimic what occurs in the course of a lifetime (ie, that GH secretion decreases with age), the need for lower doses is not surprising; however, the dosage amount varies by individual. As a result, drug trials use an empirical approach. For example, 2 or 3 adjustments over 6 months may be needed to determine the final dose. General guidelines are that women need a larger dose of GH than men,

children need more than adults, and those taking estrogen need more (especially those taking oral versus transdermal estrogen) than those who aren't on estrogen therapy.

*The Challenge of Follow Up.* Regular assessments of patients taking GH are encouraged to evaluate whether the treatment is still effective and whether reimbursement should be ongoing.

However, follow up poses unique challenges when the goal of therapy is no longer increasing linear growth. Measuring body composition can be useful to determine the effect of GH, especially for insurance coverage purposes. Lipid levels are not reliable measures, and other medications may be required to bring them down to healthy levels.<sup>5</sup> Ironically, lipid measurements are universally covered for reimbursement, but body composition measurements may not be covered. The latter are primarily used in research studies, but they provide useful data to the clinician to assess efficacy. Table 4 lists several mechanisms for measuring body composition. The biggest hurdle is the availability of the software to measure body composition. In general, the best way to assess GH efficacy is to monitor clinical symptoms and measure IGF-1 levels.<sup>5</sup>

**Coverage of Adult GH Use: Clinician and Payer Issues**

Reluctance to seek reimbursement by both endocrinologists and GH-deficient adults may occur because the physician is not aware of which conditions are reimbursable or because of healthcare plan benefit designs that exclude GH coverage in adults. As a result, undertreatment for adults is the issue as opposed to overtreatment in children.

Many clinicians and payers are concerned that if reimbursement restrictions are relaxed, GH will be used as an antiaging therapy in

**Table 4.** Methods to Measure Body Mass

<ul style="list-style-type: none"> <li>■ Dual energy X-ray absorptiometry (DEXA) scanning (special software required)</li> <li>■ Waist:hip ratio</li> <li>■ Bioimpedence</li> <li>■ Computed tomography and magnetic resonance imaging DEXA for abdominal and visceral fat</li> </ul>
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nonGH-deficient adults. This is unfortunate because GH therapy has been shown to have a tremendous impact on GH-deficient adults and should be reimbursed and considered the current standard of care. One way to address this concern is to gather all appropriate documentation and evaluate each request on a case-by-case basis.

Another complicating factor for reimbursement is that GH may not be covered under pharmacy benefit plans. As a medical benefit, payers may need to acquire the drug for members from injectable drug pharmacies and home health agencies, often at an inflated price. Some pharmaceutical companies will directly distribute GH (with all the necessary documentation provided for review), but clinicians are often unaware of

that option. This price variability affects insurance companies that pay to cover the drug and may lead to more restrictive coverage policies.

“Softer” endpoints for adult GH treatment, such as quality-of-life outcomes and the scales used for these measures, can be difficult to interpret by both clinicians and payers. Although the effect of GH treatment on body composition is impressive, and the effect of GH deficiency on cardiovascular disease is difficult to ignore, there are no clear data to show the effect GH treatment in adults has on mortality. Without data on new uses, healthcare plans at present must rely on published guidelines. However, they can also work with clinicians to collect as much data as possible for development of future coverage policies.

**Table 5.** Uninterrupted GH Therapy Versus Discontinuation of GH Treatment

Parameter	Uninterrupted GH	Discontinuation of GH
Body composition		
Percent fat	No increase	Abnormal increase
Lean body mass	No decrease	Abnormal decrease
Physical strength	Normal	Reduced
Exercise tolerance	Normal	Reduced
Bone mass	Reach peak (adult) mass	Reduced BMD
Risk of osteoporosis, fractures	Normal	Increased
Lipids: cholesterol, triglycerides	Normal	Increased
Cardiovascular morbidity and mortality	Normal	Increased
Quality of life		
Psychological impact	Positive	Negative
Educational impact	Positive	Negative
Vocational impact	Positive	Negative

BMD = Bone mineral density; GH = growth hormone.

### **GH Therapy for Transitional Patients**

Transitional patients are those who have responded well to GH treatment as children and who are being considered for continued treatment into adulthood. They are usually 15 to 18 years of age and are also transitioning from “compliant” pediatric patients to adults who are evaluating their healthcare options.

The decision to treat transitional patients is based on the answers to the following questions: What are the odds that the patient has ongoing GH deficiency? and, If the patient has ongoing GH deficiency, what are the risks of untreated GH deficiency in adulthood, especially if normal-range height has been achieved?

Between 30% and 70% of children with IGHD will have a normal GH response after GH therapy has been terminated.<sup>36,37</sup> Patients with multiple pituitary hormone deficiencies will most likely remain GH deficient, and the greater the number of pituitary deficiencies, the lower the GH response to ITT.<sup>38,39</sup> For children with IGHD who have achieved normal-range height, it may be difficult to justify continued treatment, except to avoid other cardiovascular risk factors. On the other hand, in children with ISS who have not achieved normal-range height, treatment may be considered on an individual basis, with a possible decision to administer GH treatment until the short stature is no longer debilitating.

All candidates for adult GH therapy should be assessed for ongoing GH deficiency. To do so, it is necessary to stop treatment to determine GH levels. This treatment “holiday” may require 1 year or more of observation and may pose some risks.<sup>38</sup> Extrapolation from limited available data suggests significant possible risks with discontinuation of therapy (Table 5). One study that evaluated GH-deficient and short-stature adolescents (16 to 21 years of age) who after 3

years on GH treatment discontinued treatment indicated that accumulated important cardiovascular risk factors were observed during a 2-year observation period.<sup>40</sup> Clinicians recommend continuation of therapy into adulthood to “restore normal physiology” and theoretically, prevent long-term health complications and more expensive healthcare costs overall.

Reassessment of GH deficiency after the observation period should follow the same guidelines as testing for GH deficiency in adults, although no formal guidelines have been published.

### **Coverage of Transitional Therapy: Clinician and Payer Issues**

Clinicians as well as payers are responsible for determining whether a patient should continue GH therapy, keeping in mind that patients with multiple pituitary deficiencies are most at risk. As with adult GH therapy considerations, payers and clinicians need as much data as possible on efficacy and safety; those data should include cost modeling. The transitional period will also require the development of new guidelines for use of GH in this patient population.

### **Summary**

The issues surrounding GH treatment are multifactorial and interdependent. Although clinicians and payers have traditionally viewed themselves on opposite sides of the management argument, both parties strive to “do the right clinical thing.” Recombinant therapies, particularly GH, are potentially available in almost unlimited supplies, but significant cost is associated with their use. In 1999, drug costs exceeded primary care costs for almost every managed care plan in the United States. Clearly, both clinicians and payers face the challenge of identifying the best diagnostic and eligibility criteria and the best measures of success as well as the challenge of including cost-

benefit analyses and evidence-based medicine in their decisions to treat and reimburse patients who wish to receive the latest technological advances in medicine.

... REFERENCES ...

1. Guidelines for the use of growth hormone in children with short stature: A report by the Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. *J Pediatr* 1995;127:857-867.
2. Bercu BB, Shulman D, Root AW, Spiliotis BE. Growth hormone (GH) provocative testing frequently does not reflect endogenous GH secretion. *J Clin Endocrinol Metab* 1986;63:709-716.
3. Smith WJ, Nam TJ, Underwood LE, et al. Use of insulin-like growth factor-binding protein 2 (IGFBP-2), IGFBP-3, and IGF-1 for assessing growth hormone status in short children. *J Clin Endocrinol Metab* 1993;77:1294-1299.
4. Maes M, Lindberg A, Price DA, Albertsson-Wikland K, Ranke MB. Long term growth response to growth hormone therapy in prepubertal children with idiopathic growth hormone deficiencies: Analysis of Kabi International Growth Study. In: Kabi International Growth Study biannual report. No. 11. Mannheim, Germany: J&J. Verlag; 1994:15-26.
5. Vance ML, Mauras N. Growth hormone therapy in adults and children. *N Engl J Med* 1999;341:1206-1216.
6. Boot AM, Engels MA, Boerma GJ, Krenning EP, de Muinck Keizer-Schrama SM. Changes in bone mineral density, body composition, and lipid metabolism during growth hormone (GH) treatment in children with GH deficiency. *J Clin Endocrinol Metab* 1997;82:2423-2428.
7. Kuromaru R, Kohno H, Ueyama N, Hassan HM, Honda S, Hara T. Long-term prospective study of body composition and lipid profiles during and after growth hormone (GH) treatment in children with GH deficiency: Gender-specific metabolic effects. *J Clin Endocrinol Metab* 1998;83:3890-3896.
8. Myers SE, Carrel AL, Whitman BY, Allen DB. Physical effects of growth hormone treatment in children with Prader-Willi syndrome. *Acta Paediatr* 1999;433(suppl):112-114.
9. Carrel AL, Myers SE, Whitman BY, Allen DB. Growth hormone improves body composition, fat utilization, physical strength and agility, and growth in Prader-Willi syndrome: A controlled study. *J Pediatr* 1999;134:215-221.
10. Allen DB, Fost NC. Growth hormone therapy for short stature: Panacea or Pandora's box? *J Pediatr* 1990;117:16-21.
11. Davenport ML, Punyasavatsut N, Gunther D, Savendahl L, Stewart PW. Turner syndrome: A pattern of early growth failure. *Acta Paediatr* 1999;88(suppl):118-121.
12. Rosenfeld RG, Attie KM, Frane J, et al. Growth hormone therapy of Turner's syndrome: Beneficial effect on adult height. *J Pediatr* 1998;132:319-324.
13. Plotnick L, Attie KM, Blethen SL, Sy JP. Growth hormone treatment of girls with Turner syndrome: The National Cooperative Growth Study Experience. *Pediatrics* 1998;102(2 Pt 3):479-481.
14. Sas TC, de Muinck Keizer-Schrama SM, Stijnen T, et al. Final height in girls with Turner's syndrome treated with once or twice daily growth hormone injections. Dutch Advisory Group on Growth Hormone. *Arch Dis Child* 1999;80:36-41.
15. Sas TC, de Muinck Keizer-Schrama SM, Stijnen T, et al. Normalization of height in girls with Turner syndrome after long-term growth hormone treatment: Results of a randomized dose response trial. *J Clin Endocrinol* 1999;84:4607-4612.
16. Pediatric end-stage renal disease. United States Renal Data System. *Am J Kidney Dis* 1998;32(2 suppl 1):S98-S108.
17. Fine RN, Kohaut E, Brown D, Kuntze J, Attie KM. Long-term treatment of growth retarded children with chronic renal insufficiency, with recombinant human growth hormone. *Kidney Int* 1996;49:781-785.
18. Benfield MR, Kohaut EC. Growth hormone is safe in children after renal transplantation. *J Pediatr* 1997;131(1 Pt 2):S28-S31.
19. Fine RN, Sullivan EK, Kuntze J, Blethen S, Kohaut E. The impact of recombinant human growth hormone treatment during chronic renal insufficiency on renal transplant recipients. *J Pediatr* 2000;136:376-382.
20. Guyda HJ. Growth hormone therapy for non-growth hormone-deficient children with short stature. *Curr Opin Pediatr* 1998;10:416-421.
21. Hintz RL, Attie KM, Baptista J, Roche A. Effect of growth hormone treatment on adult height of children with idiopathic short stature. The Genentech Collaborative Group. *N Engl J Med* 1999;340:502-507.
22. Attanasio AF, Lamberts SW, Matranga

- AM, et al. Adult growth hormone (GH)-deficient patients demonstrate heterogeneity between childhood onset and adult onset before and during human GH treatment. *J Clin Endocrinol Metab* 1997;82:82-88.
- 23.** Weele S. Growth hormone and insulin-like growth factor-1 as anabolic agents. *Curr Opin Clin Nutr Metab Care* 1998;1:257-262.
- 24.** Yarasheski KE. Growth hormone effects on metabolism, body composition, muscle mass, and strength. *Exercise Sport Sci Rev* 1994;22:285-312.
- 25.** Ho KK, Hoffman DM. Defining growth hormone deficiency in adults. *Metabolism* 1995;44(suppl 4):91-96.
- 26.** Consensus guidelines for the diagnosis and treatment of adults with growth hormone deficiency: Summary statement of the Growth Hormone Research Society Workshop on Adult Growth Hormone Deficiency. *J Clin Endocrinol Metab* 1998;83:379-381.
- 27.** Erfurth EM, Bulow B, Eskilsson J, Hagmar L. High incidence of cardiovascular disease and increased prevalence of cardiovascular risk factors in women with hypopituitarism not receiving growth hormone treatment: Preliminary results. *Growth Horm IGF Res* 1999;9(Suppl A):21-24.
- 28.** Markkussis V, Beshyah SA, Fisher C, Sharp P, Nicolaidis AN, Johnston DG. Detection of premature atherosclerosis by high-resolution ultrasonography in symptom-free hypopituitary adults. *Lancet* 1992;340:1188-1192.
- 29.** Merola B, Cittadini A, Colao A, et al. Cardiac structural and functional abnormalities in adult patients with growth hormone deficiency. *J Clin Endocrinol Metab* 1993;77:1658-1661.
- 30.** Longobardi S, Cuocolo A, Merola B, et al. Left ventricular function in young adults with childhood and adulthood onset growth hormone deficiency. *Clin Endocrinol (Oxf)* 1998;48:137-143.
- 31.** De Boer H, Blok GJ, Van der Veen EA. Clinical aspects of growth hormone deficiency in adults. *Endocr Rev* 1995;16:63-86.
- 32.** McGauley GA. Quality of life assessment before and after growth hormone treatment in adults with growth hormone deficiency. *Acta Paediatr Scand Suppl* 1989;356:70-72.
- 33.** Rosen T, Wiren L, Wilhelmsen L, Wiklund I, Bengtsson BA. Decreased psychological well-being in adult patients with growth hormone deficiency. *Clin Endocrinol (Oxf)* 1994;40:111-116.
- 34.** Mardh G, Lundin K, Borg G, Jonsson B, Lindeberg A. Growth hormone replacement therapy in adult hypopituitary patients with growth hormone deficiency: Combined data from 12 European placebo-controlled clinical trials. *Endocrinol Metab* 1994;1(suppl A):43-49.
- 35.** Cuneo RC, Judd S, Wallace JD, et al. The Australian multicenter trial of growth hormone (GH) treatment in GH-deficient adults. *J Clin Endocrinol Metab* 1998;83:107-116.
- 36.** Cacciari E, Tassoni P, Cicognani A, et al. Value and limits of pharmacological and physiological tests to diagnose growth hormone (GH) deficiency and predict therapy response: First and second retesting during replacement therapy of patients defined as GH deficient. *J Clin Endocrinol Metab* 1994;79:1663-1669.
- 37.** Tauber M, Moulin P, Pienkowski C, Jouret B, Rochiccioli P. Growth hormone (GH) retesting and auxological data in 131 GH-deficient patients after completion of treatment. *J Clin Endocrinol Metab* 1997;82:352-356.
- 38.** Allen DB. Issues in the transition from childhood to adult growth hormone therapy. *Pediatrics* 1999;104:1004-1010.
- 39.** Toogood AA, Shalet SM. Diagnosis of severe growth hormone (GH) deficiency in young adults who received GH replacement therapy during childhood. *Acta Paediatr* 1997;423(suppl):117-120.
- 40.** Johannsson G, Albertsson-Wikland K, Bengtsson BA. Discontinuation of growth hormone (GH) treatment: Metabolic effects in GH-deficient and GH-sufficient adolescent patients compared with control subjects. Swedish Study Group for Growth Hormone Treatment in Children. *J Clin Endocrinol Metab* 1999;84:4516-4524.

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*Implementing Optimal Guidelines for Growth Hormone Use  
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