

Developing a Rational Approach for the Use of Growth Hormone in Nonpediatric Patients

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The development of a manageable medical policy that ensures appropriate use of recombinant human growth hormone (hGH) has been elusive. Sorting through the misconceptions, fads, cosmetic uses, and economics of this therapy is difficult even for the most sophisticated medical policy or pharmacy and therapeutics committees. An effective policy enables the quick identification of appropriate patients using minimal resources. A poorly structured policy can create a hostile environment in which extra resources are spent on many members in an effort to prevent inappropriate use by a few members. The following article applies the principles of ethics, expert scientific input, and an appreciation of the economic impact each approved treatment regimen will place on the healthcare system. The roundtable faculty functioned as a medical policy committee, and the sample policies are presented to stimulate discussions within health plans to assess current growth hormone (GH) policies and challenge the standard of care while respecting the need to manage hGH proactively.

Medical Policy for Adults

Defining the appropriate adult hGH patient population is controversial. Based on the US Food and Drug Administration (FDA) labeling, published studies, and expert opinions, the panel stratified the potential uses into 4 categories:

- Approved: FDA labeled indication
- Accepted: Use supported by numerous clinical trials published in peer-reviewed journals; widely accepted use within the endocrinology community

- Possible: Medical rationale for use (less published support) is that it improves outcomes
- No Medical Rationale: Uses described in case reports or fad uses; no clinical trials available to support improvement in clinical outcomes

The objective of the committee was to prioritize uses that have documented clinical benefit in reducing morbidity and/or mortality. By employing the above criteria, the cosmetic uses of hGH were placed in the lowest categories. **Table 1** summarizes the current uses by category.

The uses in the approved and accepted categories are routinely incorporated in many medical policies of managed care organizations (MCOs). These categories represent the core of an inclusive medical policy. However, some health plans have chosen to limit their definition of appropriate use to a subset of these clinical uses based on their own review of the literature and the recommendations of local endocrinologists. The variation in covered uses leads to confusion within the provider community and may result in additional time for the plan and endocrinologist to verify plan coverage and navigate the prior authorization process. In adult patients, accepted hGH therapy included treatment of growth hormone deficiency (GHD) resulting from pituitary disease, hypothalamic disease, irradiation or trauma to the pituitary, and reconfirmed childhood GHD. In addition, GH replacement therapy for Turner syndrome, chronic renal failure, Prader-Willi syndrome, acquired immune deficiency syndrome (AIDS) wasting, and short-bowel syndrome are supported by significant clinical data. On the other hand, a host of other conditions were

considered inappropriate therapy, including fibromyalgia, chronic fatigue syndrome, and obesity, among others. The treatment of idiopathic short stature and isolated GHD were considered gray areas—areas in which treatment would be possible, but would need to be considered on a case-by-case basis.

The diagnostic workup requirements to establish GHD, as defined by medical policy, are often a source of considerable confusion and frustration. Documentation of GHD can be convoluted based on the patient presentation and the sensitivity of the test specified in the policy. A previous article in this supplement discussed the benefits and challenges associated with each test. Often MCO medical policies specify the need for 2 tests or do not specify which tests are preferred. One health plan reported a pattern of some endocrinologists to require clonidine and levodopa for their policy. Because of low specificity of these tests, a number of patients with questionable criteria have been approved. The concept of using a stringent test (ie, a test that payers and providers can rely on) is emerging. The insulin tolerance test (ITT) and/or the arginine GH-releasing hormone (GHRH) tests currently fit this description. This case illustrates that only defining when to test and the number of tests in a medical policy is not sufficient; a list of which tests are acceptable for a diagnosis needs to be included. Follow-up monitoring requirements can also be confusing. Health plans waste resources because testing requirements are not necessary, inappropriate, or place the member at undo risk.

Clearly, there is a need to develop evidence-based guidelines for the use of hGH in adults to ensure that the appropriate patients are tested for GHD and receive hGH therapy. The **Figure** displays an algorithm for the assessment and treatment of GHD in adults, based on the workshop discussion and the clinical evidence presented in this supplement.

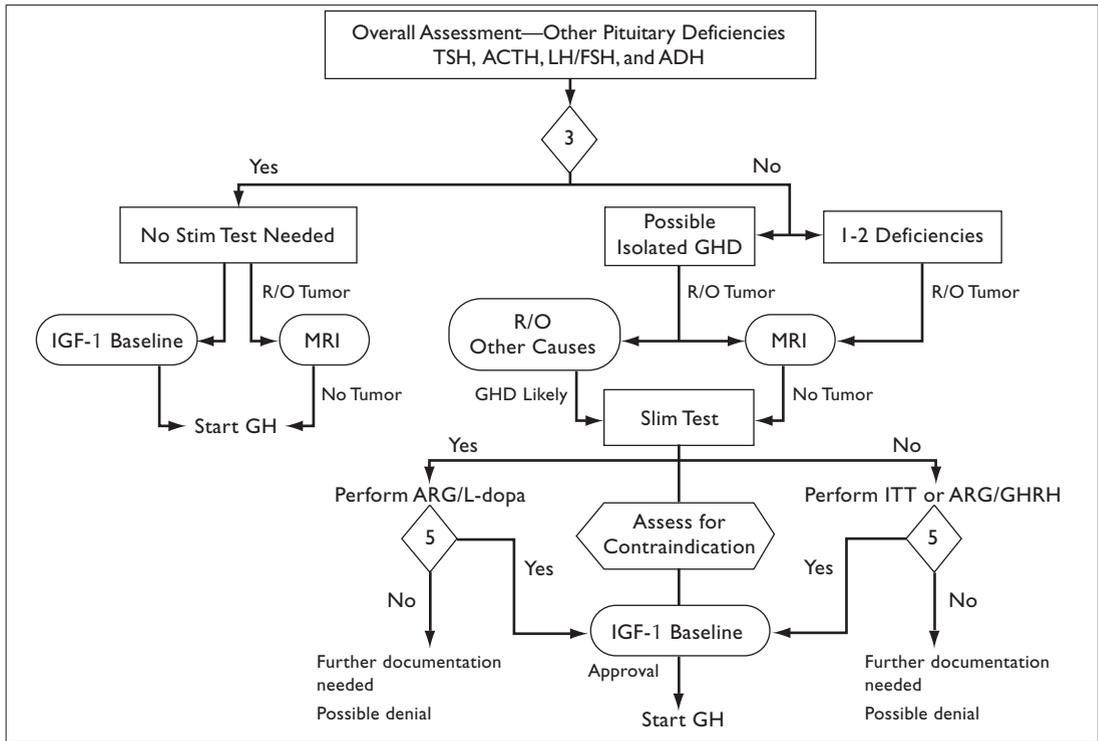
When this algorithm is coupled with the use categories listed in Table 1 and streamlined testing requirements, a degree of clarity emerges to provide an objective assessment of each potential GH patient. Limiting tests to only those with the greatest specificity and removing testing require-

Table 1. hGH Uses in Adults

Approved uses	Long-term replacement therapy in adults with GHD of either childhood- or adult-onset etiology. GHD either alone or with multiple hormone deficiencies (hypopituitarism) as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma Reconfirmed childhood GHD AIDS wasting or cachexia CRF up to time of renal transplantation Prader-Willi syndrome Turner syndrome
Accepted uses	CRF Panhypopituitarism Prader-Willi syndrome Turner syndrome AIDS wasting
Possible uses	Idiopathic short stature Isolated GHD Short-bowel syndrome
No medical rationale	Fibromyalgia Chronic fatigue Obesity Performance enhancement Short stature congenital conditions such as Down's, Fanconi's, or Bloom's syndrome Cystic fibrosis Antiaging End-stage CHF Osteoporosis Infertility Muscular dystrophy Enhanced sexual performance Regrowth of heart, liver, spleen, kidneys, and other organs that shrink with age Improved resistance to infection and cancer Faster wound healing Hair regrowth Sharper vision and hearing Mood elevation Crohn's disease

hGH indicates recombinant human growth hormone; GHD, growth hormone deficiency; AIDS, acquired immune deficiency syndrome; CRF, chronic renal failure; CHF, congestive heart failure.

Figure. Sample Adult hGH Coverage Policy Algorithm



hGH indicates recombinant human growth hormone; TSH, thyroid-stimulating hormone; ACTH, adrenocorticotropic hormone; LH/FSH, luteinizing hormone/follicle-stimulating hormone; ADH, antidiuretic hormone; GHD, growth hormone deficiency; IGF-1, insulin-like growth factor 1; MRI, magnetic resonance imaging; R/O, rule out; ITT, insulin tolerance test; ARG, adrenergic receptor variant allele; L-dopa, levodopa; GHRH, growth hormone releasing hormone.

ments in those patients with the highest probability of disease quickly identifies appropriate patients. As with all algorithms, flexibility to manage specific situations needs to be included to accommodate patients with contraindications to specific tests or an atypical GHD presentation. Obtaining an insulin-like growth factor 1 (IGF-1) level at baseline is also recommended prior to starting therapy. Since IGF-1 levels are an effective method to monitor the response to hGH therapy, this baseline level provides a monitoring mechanism that is reliable and cost effective.

Managing the Transitional Patient

The transitional population is unique because persons of the same age may be classified as pediatric, adult, or transitional. The definition of a transitional patient includes those who received hGH as a child

for a pediatric indication and those whose hGH therapy was stopped upon reaching epiphyses fusion. This definition excludes patients diagnosed with GHD later in life and recognizes these individuals as adults. Childhood-onset GHD because of anatomical damage to the pituitary, irradiation, or trauma, or the presence of panhypopituitarism is sufficient to consider continuing hGH therapy into adulthood (Table 2). However, the panel could not reach a consensus as to whether isolated GHD, long-term renal insufficiency, or the presence of Turner syndrome or Prader-Willi syndrome were compelling indications for the use of hGH in transitional patients. Other gray areas for the use of hGH in transitional patients include the treatment of short-bowel syndrome and AIDS wasting.

The primary issue is determining which individuals with known GHD in childhood

should be tested for ongoing treatment. As in the adult population, if a patient exhibits at least 3 pituitary hormone deficiencies, then provocation testing would not be clinically necessary; however, magnetic resonance imaging (MRI) and IGF-1 data should be obtained to establish baseline information of these patients. If only 1 or 2 pituitary deficiencies are present, provocation testing is warranted, preferably an ITT or arginine-GHRH. Then, an MRI should be performed as part of the workup for anterior pituitary disease, and an IGF-1 level should be obtained for baseline purposes.

Transitional patients already have a significant risk for osteopenia, an increase of visceral fat, and decreased muscle mass. Consequently, they exhibit many of the features of adult GHD. Indeed, the metabolic effects of GHD are thought to be similar in transitional and adult patients with GHD. Patients with Prader-Willi syndrome and Turner syndrome, approved indications for hGH until epiphyses fusion, should receive an evaluation of need before approval to continue for the transitional patients. Duration of therapy for transitional patients is not clear. Periodic testing using IGF-1 is suggested to determine the continued need for hGH therapy.

Conclusion

Developing an evidence-based hGH medical policy for nonpediatric patients is a complex process. In addition, medical and prescription policies are never static. There is a continual need to balance evolving scientific information and an ever-increasing requirement to manage increasing medical costs. Practice patterns vary across the country, and an assessment of the plan's provider network prescribing practices is a starting point. Understanding the patient with GH deficiency that is routinely rejected provides an initial focus for policy revision or provider education. Overly restrictive policies may actually increase the long-term cost to the health plan as the metabolic complications of GHD develop. Broad policies, on the other hand, may yield lower than expected clinical outcomes, resulting in an increased cost to the plan with no measurable improvement in clinical outcomes.

Table 2. hGH in the Transitional Patient

Approved uses	Multiple pituitary deficiencies and low IGF
Accepted uses	Child-onset GHD Pituitary tumor Pituitary surgical damage Hypothalamic disease Irradiation Trauma Reconfirmed idiopathic childhood GHD
Possible uses	Isolated GHD Turner syndrome Chronic renal insufficiency Prader-Willi syndrome AIDS wasting Short-bowel syndrome
No medical rationale	Continued height deficit at puberty Short for gestational age

hGH indicates recombinant human growth hormone; IGF, insulin-like growth factor; GHD, growth hormone deficiency; AIDS, acquired immune deficiency syndrome.

Because of emerging medical evidence highlighting the deleterious impact of GHD over a lifetime, payers and providers are beginning to recognize the importance of hGH therapy not only in the well-established pediatric setting but also in the treatment of transitional patients and adults. Transitional patients and adults with GHD are at an increased risk for metabolic disturbances that can increase morbidity and mortality and, in turn, long-term health plan costs. As the evidence is examined, the long-term benefit of this therapy may be the resolution of metabolic complications and an improvement in the quality of life for members with GHD. It is paramount for providers and payers to agree on which transitional and adult patients are appropriate for coverage and treatment. A consensus is starting to emerge among payers and providers on which transitional and adult patients should be tested for GHD, which provocation tests are most

appropriate, and who ultimately should receive hGH therapy.

A secondary consideration should be given to the approval process used by health plans. Various treatment approval forms are used by MCOs and specialty pharmacies to document an appropriate diagnosis. Some of these tools could actually limit the presentation of the clinical situation or require unnecessary tests resulting in less-than-optimal MCO decisions.

In addition, gaps exist in providers' knowledge of health plan reimbursement policies for hGH therapy. To overcome these impediments to quality cost-effective care, an efficient means for clear and consistent communication between payers and providers is clearly needed. Ideally, evidence-based guidelines should drive the use of hGH in transitional patients and adults to achieve

the goal of balancing ethical and compassionate care for these patients with the mounting need to restrain payer and member prescription costs. A policy based on FDA-approved and extensively documented uses may appear adequate but, in reality, may deprive therapy for individuals with an atypical presentation of GHD. The process must include a mechanism for a physician specialist to exercise professional judgment because the diagnostic process is not always clearly defined. An open dialogue between medical directors and endocrinologists forms the foundation for a successful policy that meets the needs of the GH population and respects the financial burden this treatment places on the MCO. The resulting policy will clearly define appropriate patients and minimize provider, payer, and member frustration.