I. Policy

Recombinant human growth hormone (GH) therapy may be considered medically necessary for the following patients:

1. Children with proven GH deficiency
2. Children with height less than the 3rd percentile for chronologic age with chronic renal insufficiency
3. Patients with AIDS wasting
4. Adults with proven GH deficiency
5. Patients with Turner’s syndrome
6. Children with growth failure due to Prader-Willi syndrome who have been evaluated for obstructive sleep apnea (OSA) and optimally treated if indicated.
7. Patients with short stature due to Noonan syndrome
8. Promotion of wound healing in burn patients
9. Prevention of growth delay in children with severe burns
10. Patients with short bowel syndrome
11. Children with short stature due to SHOX (short stature homeobox-containing gene) deficiency
12. Pediatric (i.e., age is less than five [5] years old) patients born small for gestational age (SGA), (used interchangeably with intrauterine growth restriction [IUGR]), who fail to show catch-up growth by age two (2).

The following FDA-approved indications are considered not medically necessary:

- Children with height standard deviation score of -2.25 or below
Recombinant human growth hormone is considered **investigational** for all other applications including, but not limited to the following:

- Constitutional delay (lower than expected height percentiles compared with their target height percentiles and delayed skeletal maturation when growth velocities and rates of bone age advancement are normal)
- In conjunction with gonadotropin-releasing hormone (GnRH) analogs as a treatment of precocious puberty
- GH therapy in older adults without proven deficiency
- Anabolic therapy except for AIDS provided to counteract acute or chronic catabolic illness (e.g., surgery outcomes, trauma, cancer, chronic hemodialysis, chronic infectious disease) producing catabolic (protein wasting) changes in both adult and pediatric patients
- Anabolic therapy to enhance body mass or strength for professional, recreational, or social reasons
- Glucocorticoid-induced growth failure
- Short stature due to Down’s syndrome
- Treatment of altered body habitus (e.g., buffalo hump) associated with antiviral therapy in HIV-infected patients
- Treatment of obesity
- Treatment of cystic fibrosis
- Treatment of idiopathic dilated cardiomyopathy
- Treatment of juvenile idiopathic or juvenile chronic arthritis
- Treatment of children with “genetic potential” (i.e., lower than expected height percentiles based on parents’ height)

There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this drug for these indications.

**Policy Guidelines**
The numbered guidelines correspond to the indications in the Policy section above.

**Medically Necessary Indications:**

1. Both children and adults (see No. 4 below) with proven GH deficiency are considered appropriate candidates for GH therapy.

For adults, proven GH deficiency is defined as:
a) An abnormal response to TWO provocative stimulation tests, such as L-dopa, clonidine, glucagons, arginine, GH-releasing hormone (GHRH), or insulin. The insulin tolerance test is considered the best predictor of GH deficiency; however, this test is contraindicated in patients with seizures or coronary artery disease. A provocation test using arginine and GHRH is also acceptable and is considered more stringent than tests using arginine alone or levodopa alone. Although an abnormal GH response has been traditionally defined as less than 10 ng/mL, different tests have different potencies, and the cutoff is likely to be lower when using monoclonal-based GH assays and recombinant human GH reference preparations. Twenty-four hour continuous measurements of GH, serum levels of IGF-I, or serum of levels IGFBP are considered inadequate to document GH deficiency.

b) An abnormal response to ONE provocative stimulation test in patients with defined central nervous system pathology, history of irradiation, multiple pituitary hormone deficiency, or a genetic defect.

c) Low IGF-I concentration in patients with complete hypopituitarism.

For children, no criteria have been established for the laboratory diagnosis of GH deficiency, and criteria may vary regionally. The recommended dosage for children with GH deficiency is 0.3 mg/kg per week, divided into daily or 6 times per week injections. In children, GH therapy is typically discontinued when the growth velocity is less than 2 cm per year, when epiphyseal fusion has occurred, or when the height reaches the 5th percentile of adult height.

2. Chronic renal insufficiency is defined as a serum creatinine of greater than 1.5 mg/dL (or 1.4 for women and 1.7 for men) or a creatinine clearance < 75 mL/min per 1.73 m². In patients with chronic renal failure undergoing transplantation, GH therapy is discontinued at the time of transplant or when the growth velocity is less than 2 cm per year, when epiphyseal fusion has occurred, or when the height reaches the 5th percentile of adult height.

3. AIDS (acquired immunodeficiency syndrome) wasting is defined as a greater than 10% of baseline weight loss that cannot be explained by a concurrent illness other than HIV (human immunodeficiency virus) infection. Patients treated with GH must simultaneously be treated with antiviral agents. Therapy is continued until this definition is no longer met.

4. Adults with GH deficiency are defined as in No. 1 above. Only about 25% of those children with documented GH deficiency will be found to have GH deficiency as adults. Therefore, once adult height has been achieved, subjects should be retested for GH deficiency to determine if continuing replacement therapy is necessary. These transition patients who require further treatment are usually started at doses of 0.4 to 0.8 mg/day, and titered to maintenance doses of 1.2 to 2.0 mg/day. Adults with GH deficiency not related to idiopathic deficiency of childhood (e.g., pituitary
tumor, pituitary surgical damage, irradiation, trauma) are usually started at 0.1 to 0.3 mg/day; the dose is titered to clinically desired end points (improved body composition, quality of life, reduction in cardiovascular risk factors), usually resulting in maintenance doses of 0.2 to 0.5 mg/day for men and 0.4 to 1.0 mg/day for women. The FDA cautions that the safety and effectiveness of GH therapy in adults aged 65 and over has not been evaluated in clinical studies. Therefore, it is noted that elderly patients may be more sensitive to the action of GH therapy and may be more prone to develop adverse reactions.

5. Turner’s syndrome is defined as a 45, XO genotype.

6. Prader-Willi syndrome is a genetic disorder characterized by a microdeletion in the long arm of chromosome 15. Clinically, the syndrome presents as a complex multisystem disorder characterized by excessive appetite, obesity, short stature, characteristic appearance, developmental disability, and significant behavioral dysfunction. GH deficiency has been demonstrated in most tested patients with Prader-Willi syndrome.

   Sleep studies are recommended prior to initiation of growth hormone therapy for obese paediatric patients with Prader-Willi syndrome.

7. GH therapy for burn patients should be limited to those patients with 3rd-degree burns.

8. Children with severe burns have been successfully treated with 0.05 to 0.2 mg/kg rhGH per day during acute hospitalization and for up to 1 year after burn.

9. Growth hormone for patients with short bowel syndrome should be limited to patients receiving specialized nutritional support in conjunction with optimal management of short bowel syndrome. Specialized nutritional support may consist of a high-carbohydrate, low-fat diet adjusted for individual patient requirements. Optimal management may include dietary adjustments, enteral feedings, parenteral nutrition, fluid, and micronutrient supplements. Zorbtive is administered daily at 0.1mg/kg subcutaneously up to 8 mg/day. Administration of Zorbtive for longer than 4 weeks has not been adequately studied per the FDA indications.

Note: Regarding pediatric patients who are small for gestational age with failure to catch up by age 2, the mean height of the pediatric patient must be at least two (2) standard deviations below the mean. Beyond the first year of treatment, this will be considered medically necessary provided that the treatment of the first year shows a benefit indicating that there will be a response in the second year. (Absence of catch-up growth is defined as a height velocity below one (1) standard deviation score, adjusted for age.)
Short stature" has been defined by the American Association of Clinical Endocrinologists and the Growth Hormone Research Society as height more than 2 SD below the mean for age and sex.

Cross-references:
MP-2.130 Somatostatin Analogues (Lanreotide and Octreotide)
MP-2.103 Off-Label Use of Medications

II. PRODUCT VARIATIONS

[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

[N] Capital Cares for Kids  [N] Indemnity
[N] PPO  [N] SpecialCare
[N] HMO  [N] POS
[N] SeniorBlue HMO (see note)  [Y] FEP PPO*
[N] SeniorBlue PPO (see note)  

*Refer to FEP Medical Policy Manual:

- MP-5.08.11 Growth Hormones – Adult (somatotropin)
- MP-5.08.12 Growth Hormones- Child (somatotropin)
- MP 5.08.23 Tev-Tropin- PediatricGH
- MP-5.08.08 Genotropin- Pediatric GH
- MP-5.08.18 Norditropin-Pediatric GH
- MP-5.08.19 Nutropin-Pediatric GH
- MP-5.08.20 Omnitrope- Pediatric GH
- MP-5.08.21 Saizen-Pediatric GH

The FEP Medical Policy manual can be found at: www.fepblue.org

Note: FDA approved drugs used for indications other than what is indicated on the FDA approved product label may be covered under Medicare if it is determined that the use is medically accepted, taking into consideration the Medicare recognized national drug compendia, authoritative medical literature and/or accepted standards of medical practice.” Refer to Medicare Benefit Policy Manual (100-2, Chapter 15, Section 50.4.2- Unlabeled Use of Drug). http://www.cms.gov/manuals/Downloads/bp102c15.pdf
III. DESCRIPTION/BACKGROUND

Recombinant human growth hormone (GH) is FDA approved for a variety of indications and is also proposed for various non-labeled indications such as cystic fibrosis and treatment of older adults without documented GH deficiency.

Human growth hormone (GH), also known as somatotropin, is synthesized in somatotropic cells of the anterior lobe of the pituitary gland. GHD can occur due to a variety of conditions, such as:

- Pituitary tumor
- Pituitary dysfunction due to prior surgery or radiation treatment
- Extrapituitary tumor
- Sarcoidosis, and/or other infiltrating disorders
- Idiopathic

GHD in children is manifested primarily by short stature. In adults, as well as in some children, other abnormalities associated with GHD are often evident. These include changes in body composition, higher levels of low-density lipoprotein (LDL) cholesterol, lower bone density, and a decreased self-reported quality of life compared with healthy peers. Some evidence also suggests that there may be increases in cardiovascular disease and overall mortality, but it is less clear whether growth hormone deficiency is causative for these outcomes.

Beginning in 1985, recombinant GH has been marketed for a variety of U.S. Food and Drug Administration (FDA) -labeled indications in Table 1.

Table 1 FDA-Approved Indications by Product

<table>
<thead>
<tr>
<th>Indications</th>
<th>Genotropin (Pfizer)</th>
<th>Humatrope (Lilly)</th>
<th>Norditropin (Novo-Nordisk)</th>
<th>Nutropin (Genentech)</th>
<th>Saizen (Serono)</th>
<th>Serostim (Serono)</th>
<th>Tev-Tropin Zomacton* (Ferring)</th>
<th>Zomacton* (Ferring)</th>
<th>Omnitrope (Sandoz)</th>
<th>Zorbtive (Serono)</th>
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</thead>
<tbody>
<tr>
<td>Growth failure, pediatrics patients with inadequate endogenous GH</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Growth failure due to Prader-Willi syndrome</td>
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<tr>
<td>Replacement therapy in adults with GHD</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
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<tr>
<td>HIV wasting or cachexia</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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</tr>
<tr>
<td>Children born small for gestational age, who fail to show catch-up growth by age 2 y</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Short stature (height * SDS ≤ -2.25) in non-GHD pediatrics patients</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Short stature due to Turner syndrome</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

*Zomacton is not available in the U.S.
**MEDICAL POLICY**

<table>
<thead>
<tr>
<th>POLICY TITLE</th>
<th>HUMAN GROWTH HORMONE</th>
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</tr>
<tr>
<td>POLICY NUMBER</td>
<td>MP-2.109</td>
</tr>
</tbody>
</table>

(45,XO)

<table>
<thead>
<tr>
<th>Treatment of short bowel syndrome</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Short stature in pediatrics patients with SHOX deficiency</td>
<td>Yes</td>
</tr>
<tr>
<td>Noonan syndrome</td>
<td></td>
</tr>
</tbody>
</table>

FD... SHOX: short stature homeobox-containing gene.

*On March 31, 2015, the Food and Drug Administration approved a name change for Tev-Tropin; Tev-Tropin is now known as Zomacton.

Major points of controversy are what defines “inadequate secretion of normal endogenous growth hormone,” and what constitutes “growth failure.” Before the availability of biosynthetic GH, GH was rationed to children with classic GHD, as defined by a subnormal response (<10 ng/mL, approximately, depending on GH assay) to GH provocation tests. However, the ready supply of GH has created interest in expanding its use to short-stature children without classic GHD, often referred to as partial GHD, neurosecretory GH dysfunction, constitutional delay in growth and development, or idiopathic short stature. “Classic” GHD is suggested when the abnormal growth velocity (typically <10th percentile) or height is more than 2 SDS below the current population mean, in conjunction with a chronologic age that is greater than the height age and bone age. Practically, interest in broadening the use of GH to non-GHD children has resulted in GH evaluation in many children who are simply below the 3rd percentile in height, with or without an abnormal growth velocity.

These broadened patient selection criteria have remained controversial due to uncertainties in almost every step in the diagnosis and treatment process—selection of patients to be tested, limitations in the laboratory testing for GH, establishment of diagnostic cutoffs for normal versus abnormal GH levels, availability of the laboratory tests to predict response to GH therapy, changes in growth velocity due to GH therapy, whether resulting final height is significantly improved, and whether this improvement is clinically or emotionally significant for the patient. In addition, there are many ethical considerations regarding GH therapy, most prominently appropriate informed consent when the therapy is primarily requested by parents due to their particular psychosocial concerns about height.

In 2001, Genotropin received an FDA-labeled indication for treatment of pediatric patients born small for gestational age who failed to show catch-up growth by age 2 years. Most children born small for gestational age normalize their stature during infancy, but about 15% maintain an exceptionally short stature at least throughout childhood. Epidemiologic surveys have suggested that the average adult height of men and women who did not exhibit catch-up growth as children is 5 feet, 6 inches, in men and 5 feet, 1 inch, in women. GH has been investigated in these children, based in part on the hypothesis that a GH resistance is a possible etiology of the growth restriction. In 2003, FDA approved a rhGH product for use in non-GH-deficient short stature, defined by the manufacturer as a height SDS of -2.25 below the mean. This indication for GH is the first indication based on short stature alone, without an underlying etiology.
IV. **Rationale**

**Outcome Measures in Growth Hormone Research**

The most common outcome measure reported in growth hormone (GH) research is change in height. For some situations, such as in patients with documented growth hormone deficiency (GHD) or genetic disorder and short stature, improvements in height alone may be a sufficient outcome measure. However, in most situations, a change in height is not in itself sufficient to demonstrate that health outcomes are improved. There is not sufficient evidence to establish that short stature is associated with substantial impairments in psychological functioning or quality of life, nor is there evidence that increases in height improve these parameters. Similarly, improvements in other measures of body composition such as muscle mass or muscle strength are not in themselves sufficient to establish that health outcomes are improved. Therefore, for most conditions in this literature review, changes in other outcome measures, such as functional status, quality of life, or disease-specific clinical outcomes, are necessary to demonstrate an improvement in health outcomes.

**Safety of GH Treatment**

Adverse effects (AEs) can occur with GH treatment. In children, increased rates of skeletal problems such as worsening of scoliosis can occur in association with a rapid growth spurt. In adults, arthralgias, edema, and carpal tunnel syndrome are common. Less common AEs include pancreatitis and gynecomastia.\(^1,2\)

There is concern that GH treatment may increase the rate of malignancy, particularly de novo leukemia in patients without risk factors. To date, there is insufficient evidence of a causative relation between GH treatment and malignancy rates. The largest study published to date on the association of GH treatment with malignancy includes data on 54,996 included in a postmarketing surveillance registry established by Genentech Inc.\(^3\) The most common indications for GH use among children in the database were idiopathic GHD (42.5%), idiopathic short stature (17.8%), organic GHD (15.2%), and Turner syndrome (9.3%). As of January 1, 2006, a total of 4084 AEs (6.2%), including 1559 (2.4%) serious adverse events (SAEs) and 174 (0.3%) deaths, had been reported. Investigators assessed 19 of 174 deaths (11% of deaths) as related to GH treatment. Twelve of the 19 GH-associated deaths were due to neoplasms (0.1% of children in the registry); the other 7 deaths were each due to a different cause. Overall, intracranial malignancies of nonpituitary origin were reported in 243 patients; 44 were new-onset malignancies. In addition, extracranial malignancies, including leukemia, were reported in 87 patients; 63 were new-onset extracranial malignancies. The authors reported that 36 new-onset malignancies (intracranial and extracranial combined) occurred in individuals without risk factors; 29 of the 36 cases were confirmed as being enrolled in the registry. The rate of new-onset malignancy did not exceed the rate expected in the general population (standard incidence ratio, 1.12; 95% confidence interval [CI], 0.75 to 1.61). This study lacked a concurrent comparison with untreated patients to compare actual rates of malignancy and other adverse events.
In addition, a 2014 study did not find an increased risk of de novo malignancies in GH-treated patients who survived childhood cancer for at least 5 years. The study included 12,098 patients in the United States and Canada; 338 (2.8%) were verified users of GH treatment. Sixteen of 338 (4.7%) of GH-treated survivors and 203 (1.7%) non-GHD-treated survivors developed cancers of the central nervous system; the difference between groups was not statistically significant.

Several publications on the safety of GH therapy used French registry data and vital statistics. A 2012 analysis of long-term mortality after GH treatment was conducted by Carel et al. A total of 6928 children were included in the study. Indications for GH therapy included idiopathic isolated GHD (n=5162), neurosecretory dysfunction (n=534), idiopathic short stature (n=871), and born small for gestational age (n=335). The mean dose of GH used was 25 μg/kg/d and the mean treatment duration was 3.9 years. Patients were followed for a mean of 17.3 years. As of September 2009, follow-up data on vital status were available for 6558 (94.7%) of participants. Ninety-three of the 6558 individuals (1.42%) had died. The mortality rate was significantly higher in patients treated with GH than would be expected on the basis of year, sex, or age (standardized mortality ratio, 1.33; 95% CI, 1.08 to 1.64). Cox survival analysis found that male sex and higher dose of GH were independent predictors of mortality risk. Examination of the causes of death found a significant increase in mortality due to circulatory system diseases. In addition, there was a significant increase in the number of deaths due to bone tumors (3 observed deaths vs 0.6 expected deaths) but no other types of cancers or overall cancer deaths. There was also a significant increase in the number of deaths due to cerebral or subarachnoid hemorrhage (4 observed deaths vs 0.6 expected). In 2014, Poidvin et al reported on the same data, focusing on risk of stroke in adulthood among childhood users of GH therapy. This analysis included 6874 children with idiopathic isolated GHD or short stature; mean length of follow-up was 17.4 years. There were 11 (0.16%) validated cases of stroke and the mean age at the time of stroke was 24 years. Risk of stroke was significantly higher in adults who had used GH than in general population controls. Stroke risk was also compared with general population controls. Standard incidence ratios were 2.2 (95% CI, 1.3 to 3.6) compared with registry data from Dijon and 5.3 (95% CI, 3.0 to 8.5) using Oxford registry data. The increased risk was largely for hemorrhagic stroke (8/11 cases), and this elevated risk persisted when the 3 patients who had been small for gestational age were excluded from the analysis. In both of the previous analyses from this research team, there were a small number of events (ie, deaths or stroke), and thus conclusions from these data are not definitive on the long-term safety of GH therapy.

Growth Hormone Deficiency
Once a true GHD has been established in association with clinical symptoms of GHD, there is a compelling rationale for treatment with exogenous GH. Randomized controlled trials (RCTs) support the benefits of GH replacement in terms of increasing height and alleviating secondary effects of GHD. A few representative trials are discussed next.

GHD in Children
In children with GHD, treatment increases growth velocity and final height. Root et al followed approximately 20,000 children for 9 years as part of the National Cooperative Growth Study. Growth velocity improved compared with pretreatment values, and this improvement was
maintained for at least 4 years. For children treated for at least 7 years, improvements in the mean height standard deviation score (SDS) ranged from 1.3 to 2.5, depending on the specific underlying condition. If treatment is started at an early age, most children can achieve a final height close to that expected from parental height. In a study of 1258 patients in the Pfizer International Growth Database, the standard deviation (SD) for differences between the final height achieved and the midrange of predicted height from parental values ranged between -0.6 and +0.2, depending on the specific underlying condition.  

**GHD in Adults**

In adults with GHD, evidence from RCTs shows that treatment leads to increases in lean body mass and decreases in body fat. Meta-analyses of RCTs have shown evidence for increases in muscle strength and exercise capacity, although this was not a robust finding across all studies. There is also evidence from meta-analyses that GH therapy is associated with increased bone mineral density (BMD) in adults with GHD. For example, a 2014 meta-analysis by Barake et al identified 9 placebo-controlled RCTs with at least 1-year follow-up on the effect of daily GH therapy on BMD. Analysis of RCT data found a statistically significant increase in BMD of the lumbar spine and femoral neck in patients with GHD who received GH therapy for more than 2 months. Change in BMD ranged from 1% to 5% at the spine and 0.6% to 4% at the femoral neck. A limitation of the Barake analysis is that data were not available on fracture rates, a clinically important outcome. The evidence on other outcomes, such as quality of life, lipid profiles, cardiovascular disease, and total mortality, is not consistent and is insufficient to determine whether these outcomes are improved with treatment.

**Growth Failure due to Prader-Willi Syndrome**

Most children with Prader-Willi syndrome have hypothalamic dysfunction and are GH deficient. Use of human GH for children with growth failure due to Prader-Willi syndrome is an Food and Drug Administration (FDA) ‒ approved indication. The value of testing for GHD before treatment in these patients is questionable. None of the clinical studies selected patients for treatment based on presence or absence of GHD, nor were results reported separately for those with or without GHD. Information from the product label indicates that the height SDS for Prader-Willi syndrome children in the clinical studies was -1.6 or less (height was in the 10th percentile or lower).

Several RCTs in children have shown patient improvements with use of GH. For example, a 2008 RCT published by Festen et al included 42 infants and 49 prepubertal children (age range, 3-14 years) and found that GH treatment significantly improved height, body mass index, head circumference, and body composition. In 2012, the same investigators published cognitive outcomes in children participating in this trial. During the 2-year randomized study, the mean total IQ score and subtests did not change significantly from baseline in GH-treated children. In untreated children, there was no significant change in total IQ score, but scores on 2 of 3 subtests significantly declined from baseline.

Moreover, a 2013 RCT found that the addition of GH therapy to physical training resulted in greater improvements in motor development than physical training alone. This was a 2-year,
single-blind trial that included 22 children newly diagnosed with Prader-Willi syndrome (mean age, 12.9 months). Outcomes were evaluated every 3 months and multiple regression analysis was conducted to evaluate whether GH had an impact on motor development over time. Among the results was the finding that GH had statistically significant interaction effects on a model predicting motor development age using the Alberta Infant Motor Scale.

According to the drug prescribing information, GH therapy use has been associated with sudden death in children with Prader-Willi syndrome.21 These deaths occurred among children who were severely obese or had severe respiratory impairment; these markers are now considered to be contraindications to GH treatment use.

For adults with Prader-Willi syndrome, the benefits of GH treatment are less apparent, and treatment is not an FDA-approved indication for GH (Genotropin). In 2012, Sode-Carlsen et al in Scandinavia published an RCT evaluating GH therapy in 46 adults with genetically confirmed Prader-Willi syndrome.22 Patients were randomized to receive 12 months of GH treatment or placebo. The authors reported a number of outcomes related to body composition and laboratory test results; they did not specify a primary outcome. In addition, the authors primarily reported within-group outcomes. For example, in the GH-treated group, after 1 year, lean body mass increased a mean of 2.25 kg (p=0.005 vs baseline), and fat mass decreased by a mean of 4.2 kg (p<0.001 vs baseline). In the same time period, there was no significant change in lean body mass in the placebo group and a significant increase (p<0.001) in fat mass (change in kilograms was not reported for the placebo group). During the 12-month treatment period, no significant changes were found in either group for other variables including in levels of high-density lipoprotein cholesterol or triglycerides, peak expiratory flow, fasting glucose, fasting insulin, and physical function. However, the level of low-density lipoprotein–cholesterol decreased significantly more in the GH-treated than in the control group (mean difference [MD], 0.27 mmol/L, p=0.047). This study presents insufficient evidence that GH therapy is effective for improving health outcomes in adults with Prader-Willi syndrome.

**Section Summary: Growth Hormone Deficiency**

For patients with documented GHD and clinical manifestations such as short stature, GH replacement has been shown to improve growth velocity and final height achieved. In addition, it can ameliorate the secondary manifestations of GHD seen primarily in older children and adults.

**Conditions Without GHD**

**Children With Short Stature Associated With Chronic Renal Insufficiency**

In 2013, Wu et al published a meta-analysis of RCTs evaluating the impact of GH therapy on height outcomes following renal transplant in children age 0 to 18 years.23 Five trials with a total of 401 participants met the review’s inclusion criteria (RCTs including renal allograft recipients between 0 and 18 years old). Trials were published between 1996 and 2002. A meta-analysis found significantly improved height velocity at the end of a year in children taking GH compared with a no treatment control group. At the beginning of the year, both groups had a negative height SDS, with no statistically significant differences between groups. After 1 year, the pooled
MD in height SDS was 0.68 (95% CI, 0.25 to 1.11; p=0.002) in favor of the GH group. There were no statistically significant differences between groups in the rate of rejection episodes or in renal function.

Previously, in 2012, Hodson et al published a Cochrane review of RCTs evaluating GH treatment in children with chronic kidney disease. To be included in the review, trials needed to include children 18 years old or younger who were diagnosed with chronic kidney disease and were predialysis, on dialysis, or posttransplant. In addition, trials needed to compare GH treatment with placebo, no treatment, or a different GH regimen, and needed to include height outcomes. A total of 7 RCTs with 809 children met the review criteria. Study entry criteria varied (eg, ranging from <3rd percentile for chronological age to <50th percentile for chronological age). Overall, treatment with GH (28 IU/m²/wk) compared with placebo or no specific therapy resulted in a statistically significant increase in height SDS at 1 year (8 studies; MD=0.82; 95% CI, 0.56 to 1.07). Moreover, a pooled analysis of 7 studies found a significant increase in height velocity at 1 year in the group receiving GH treatment compared with control (MD=3.88 cm/y; 95% CI, 3.32 to 4.44).

An example of an individual RCT is Hokken-Koelega et al, conducted in the Netherlands. This was a double-blind, placebo-controlled crossover trial in 20 prepubertal children with severe growth restriction and chronic renal failure. Entry criteria included height velocity less than the 25% percentile for chronological age. Patients received 6 months of subcutaneous injection of GH (4 IU/m²/d) before or after 6 months of placebo injection. There was a 2.9 cm greater increase in height velocity per 6 months with GH than with placebo. Long-term follow-up data on children in this and other Dutch RCTs (maximum of 8 years of treatment) were published in 2000. GH treatment resulted in significant improvement in the height SDS compared with baseline scores (p<0.001). Moreover, the mean height SDS reached the lower end (-2 SDS) of the normal growth chart after 3 years of treatment. Puberty began at a median age within the normal range for girls and boys, and GH therapy did not result in significant effects on parathyroid hormone concentration, and there were no radiologic signs of renal osteodystrophy.

**Turner Syndrome**

Short stature is almost universal in Turner syndrome. Poor growth is evident in utero and further deceleration occurs during childhood and at adolescence. The mean adult height for those with Turner syndrome is 58 inches (4 feet, 10 inches). Unlike Prader-Willi syndrome, GHD is not seen. FDA approvals for GH were based on the results of RCTs that included final adult height as the outcome. For example, a group of patients with Turner syndrome given somatropin (Humatrope) at a dosage of 0.3 mg/kg/wk for a median of 4.7 years achieved a final height of 146.0±6.2 cm (57.5±2.25 in) compared with an untreated control group who achieved a final height of 142.1±4.8 cm (56±2 in).

In 2007, a Cochrane review identified 4 RCTs (total N=365) evaluating GH for treating Turner syndrome. Studies included children who had not yet achieved final height, treated children for at least 6 months, and compared GH with placebo or no treatment. Only 1 trial reported final height, so outcomes could not be pooled. A pooled analysis of 2 trials found that short-term
growth velocity was greater in treated than in untreated children (MD=3 cm/y; 95% CI, 2 to 4 cm/y).

**Short Stature Due to Noonan Syndrome**

In 2015, Giacomozzi et al published a systematic review of literature on the effect of GH therapy on adult height.\(^{29}\) Included in the review were studies treating individuals with a diagnosis of Noonan syndrome with no other causes of short stature and a normal karyotype in females. In addition, studies needed to follow patients for at least 3 years. A total of 23 studies met the inclusion criteria; none were RCTs and only 1 was controlled. Three of the studies were case reports and the remainder prospective or retrospective cohort studies. In the 1 controlled study (MacFarlane et al\(^{30}\)), over the 3-year follow-up, the GH treated group gained a mean of 3.3 cm more than the untreated group. Among the uncontrolled studies, 2 reported adult height. Mean height SDS was -2.8 (SD=0.6) and mean adult height SDS was -1.4 (SD=0.9). Two uncontrolled studies reported near-adult height, which was -2.1 (SD=0.9). In addition, 2 studies reported a change in height SDS corresponding to 8.6 cm (SD=5.9). The data are limited by the paucity of controlled studies and lack of RCTs.

**Children With Short Stature due to Short Stature Homeobox-Containing Gene Deficiency**

Treatment of children with short stature due to short stature homeobox-containing gen (SHOX) deficiency is an FDA-approved indication for GH therapy (Humatrope).\(^{27}\) A 2010 Health Technology Assessment on GH treatment of growth disorders in children conducted a systematic review and identified 1 RCT evaluating GH therapy for children with short stature due to SHOX.\(^{31}\) This industry-sponsored, open-label multicenter study was published by Blum et al in 2007.\(^{32}\) It included 52 prepubertal children age at least 3 years who had SHOX deficiency. Height requirements were less than the 3rd percentile of the local reference range or less than 10th percentile with height velocity less than the 25th percentile. Participants were randomized to receive 2 years of GH treatment (n=27) or usual care (n=25). The primary outcome was first-year height velocity. Fifty-one of 52 patients completed the study. The first-year height velocity was 8.7 cm/y (SD=0.3) in the GH therapy group and 5.2 cm/y (SD=0.2) in the untreated group; the difference between groups was statistically significant (p<0.001). Height gain over the 2-year treatment period was 16.4 (SD=0.4) cm in the treatment group and 10.5 (0.4) cm in the untreated group (p<0.001). No SAEs were reported for either group.

**Treatment of Severe Burns**

A Cochrane systematic review, published in 2012, included RCTs evaluating the impact GH therapy on the healing rate of burn wounds.\(^{33}\) Thirteen trials were identified that compared GH therapy with another intervention or to placebo. Six included only children and 7 involved only adults. Twelve of the studies were placebo-controlled. Findings of 2 studies reporting wound healing time in days were pooled. The mean healing time was significantly lower in the GH-treated group compared with placebo (MD=9.07 days; 95% CI, -4.39 to -13.76). The authors also conducted meta-analyses of studies that did not conduct survival analyses but did follow patients until their wounds healed. These analyses found significantly shorter healing time in patients who received GH therapy among adults (2 studies) and among children (2 studies). A
pooled analysis of 5 studies did not find a statistically significant difference in mortality among patients receiving GH therapy and placebo (risk ratio [RR], 0.53; 95% CI, 0.22 to 1.29). The mortality analysis was likely underpowered; the total number of deaths was 17. A pooled analysis of 3 studies involving adults found significantly shorter hospital stays in patients who received GH therapy compared with placebo (MD = -12.55 days; 95% CI, -17.09 to -8.00). In another pooled analysis, there was a significantly higher incidence of hyperglycemia in GH-treated patients than in controls (RR=2.65; 95% CI, 1.68 to 4.16).

One RCT measuring mortality included 54 adult burn patients who survived the first 7 postburn days. Those patients showing difficulty with wound healing were treated with recombinant human growth hormone (rhGH) and compared with those healing at the expected rate with standard therapy. Mortality of rhGH-treated patients was 11% compared with 37% not receiving rhGH (p=0.027). Infection rates were similar in both groups. Singh et al studied 2 groups of patients (n=22) with comparable third-degree burns; those who received GH had improved wound healing and lower mortality (8% vs. 44%). Another placebo-controlled trial found no benefit to GH with regard to length of hospitalization in 24 adult patients with severe burns.

**Prevention of Growth Delay in Children With Severe Burns**

Children with severe burns show significant growth delays for up to 3 years after injury. GH treatment in 72 severely burned children for 1 year after discharge from intensive care resulted in significantly increased height in a placebo-controlled, randomized, double-blinded trial. Aili Low et al found that GH treatment in severely burned children during hospitalization resulted in significantly greater height velocity during the first 2 years after burn compared with a similar group of untreated children.

**Treatment of HIV Wasting**

In 2004, Moyle et al published a systematic review of controlled and uncontrolled studies on selected treatments of HIV wasting. To be included, studies needed to include more than 10 patients and have a treatment duration of at least 2 weeks. Studies of GH therapy showed significant increases in lean body mass compared with placebo. Two of the studies evaluating GH treatment found statistically significant improvements in some aspects of quality of life after 12 weeks.

**GH Therapy in Conjunction With Optimal Management of Short Bowel Syndrome**

Short bowel syndrome is experienced by patients who have had half or more of the small intestine removed with resulting malnourishment because the remaining small intestine is unable to absorb enough water, vitamins, and other nutrients from food. The FDA label for Zorbttive indicates that GH has been shown in human clinical trials to enhance the transmucosal transport of water, electrolytes, and nutrients. According to the product label, FDA approval for Zorbttive was based on the results of a randomized, controlled, phase 3 trial in which patients dependent on intravenous parenteral nutrition who received Zorbttive (either with or without glutamine) over a 4-week period had significantly greater reductions in the weekly total volume of intravenous parenteral nutrition required for nutritional support. However, the effects beyond 4 weeks were not evaluated nor were treatment locations (inpatient vs outpatient) identified.
A 2010 Cochrane review identified 5 RCTs evaluating GH therapy for treating short bowel syndrome.\textsuperscript{40} Studies evaluated GH with or without glutamine treatment. The primary outcome was change in body weight. A pooled analysis of 3 small trials (total N=30) found a statistically significant difference in weight change when patients were treated with GH or placebo (MD=1.66 kg; 95% CI, 0.69 to 2.63; p<0.001).

Several published studies have also demonstrated improved intestinal absorption in short bowel syndrome patients receiving parenteral nutrition.\textsuperscript{41,42} However, studies have noted that the effects of increased intestinal absorption are limited to the treatment period.\textsuperscript{42,43} Specialized clinics may offer intestinal rehabilitation for patients with short bowel syndrome; GH may be 1 component of this therapy.

**Small for Gestational Age Children**

A meta-analysis of RCTs evaluating GH treatment for children born small for gestational age was published in 2009.\textsuperscript{44} Four trials with a total of 391 children met the eligibility criteria (birth height or weight <2 SDS, initial height <2 SDS). The GH dose ranged from 33 to 67 μg/kg in the RCTs, and mean duration of treatment was 7.3 years. Mean adult height in the 4 studies was -1.5 SDS in the treated group and -2.4 SDS in the untreated group. Adult height in the treated group was significantly higher than that of controls (MD=0.9 SDS [5.7 cm]; p<0.001). There was no difference in adult height between the 2 doses of 33 and 67 μg/kg/d. The authors commented that it is unclear whether the gain in adult height associated with GH treatment “is of sufficient clinical importance and value to warrant wide-spread treatment of short children born SGA [small for gestational age].”

There are very few data on the psychosocial outcomes of short pediatric or adult stature related to intrauterine growth restriction and how these outcomes may be affected by GH therapy. As noted, data are inadequate to document that short-stature youths have either low self-esteem or a higher than average number of behavioral or emotional problems.

For both small for gestational age children and short-stature children, an additional strategy to achieve target adult heights is combining GH therapy with gonadotropin hormone–releasing (GnRH) analogs, which prolongs the prepubertal growth period. The combination therapy is intended to increase the critical pubertal height gain by delaying the fusion of the epiphyseal growth plates, thus prolonging the period during which GH is active. This therapy has been suggested for children who are considered short when they enter puberty.\textsuperscript{45-47}

**Altered Body Habitus Related to Antiretroviral Therapy for HIV Infection**

There is research on the use of GH for altered body habitus that may be a complication of antiretroviral therapy for HIV infection. Body habitus changes, also referred to as the fat redistribution syndrome, include thinning of the face, thinning of the extremities, truncal obesity, breast enlargement, or an increased dorsocervical fat pad (“buffalo hump”).\textsuperscript{48} However, there is scant published literature on the use of GH for this indication. The literature is dominated by letters to the editors and small case series. The largest case series was reported by Wanke et al who treated 10 HIV-infected patients with fat redistribution syndrome with GH for 3 months.\textsuperscript{49} The authors reported improved waist/hip ratio and mid-thigh circumference.
Children With Idiopathic Short Stature (ie, Without Documented GHD or Underlying Pathology)

**Impact of GH Treatment on Adult Height of Children With Idiopathic Short Stature**

Several meta-analyses have been published. Most recently, in 2011, Deodati and Cianfarani identified 3 RCTs and 7 non-RCTs. Selection criteria for the meta-analysis, included prepubertal children with initial short stature (>2 SD below the mean) and peak GH response greater than 10 μg/L. In addition, participants could not have had previous GH therapy or comorbid conditions that could impair growth. Adult height was defined as a growth rate of less than 1.5 cm/y or bone age was 15 years in females and 16 years in adults. The primary efficacy outcome was the difference between groups in adult height; this was measured as an SDS (also known as a z score). The investigators considered an MD in height of more than 0.9 SDS (≈6 cm) to be a satisfactory response to GH therapy. Only 1 of the RCTs was placebo-controlled, and that study had a high dropout rate (40% in the treated group, 65% in the placebo group).

In the 3 RCTs (total N=115), the mean adult height (primary efficacy outcome) was -1.52 SDS for treated children and -2.30 SDS for untreated children. The difference between groups significantly favored the treated group (MD=0.65 SDS [≈4 cm]; 95% CI, 0.40 to 0.91; p<0.001). The mean adult height in the 7 nonrandomized studies was -1.7 SDS for treated children and -2.1 SDS for untreated children. The MD between groups was 0.45 SDS (3 cm) (95% CI, 0.18 to 0.73) and was statistically significant favoring the treated group (p<0.001). Although GH treatment resulted in a statistically significant increase in adult height in the treated group, according to the a priori definition of a satisfactory response, the difference was not clinically significant. Moreover, there was a lack of high-quality, placebo-controlled RCTs.

In 2009, a Cochrane review by Bryant et al evaluated GH therapy for idiopathic short stature in children and adolescents. A total of 10 RCTs met eligibility criteria, which included being conducted in children who had normal GH secretion, normal size for gestational age at birth, and no evidence of chronic organic disease. In addition, studies needed to compare GH treatment with placebo or no treatment and provide GH treatment for at least 6 months. Three studies were placebo-controlled, and the other 7 compared GH therapy with no treatment. Unlike the Deodati and Cianfarani review previously described, studies were not required to report final adult height. Nine of 10 studies in the Cochrane review were short term and reported intermediate outcomes. A pooled analysis of 3 studies reporting growth velocity at 1 year found a statistically significantly greater growth velocity in treated than in untreated children. The WMD was 2.84 (95% CI, 2.06 to 2.90). Five studies reported height SDSs, but there was heterogeneity among studies and the findings were not pooled. These data suggest that GH has an effect on height in children with idiopathic short stature in the short term but that evidence on GH’s effects on adult height is extremely limited.

**Section Summary: Impact of GH Treatment on Adult Height of Children With Idiopathic Short Stature**

Systematic reviews have found that GH treatment may increase height gain for children with idiopathic short stature, but the difference in height gain may not be clinically significant. The
absolute difference in height in these studies ranged from 3 to 4 cm, and children treated with
GH remained below average in height, with heights between 1 and 2 SD below the mean at the
end of treatment. These studies did not follow treated patients long enough to determine the
ultimate impact of GH on final adult height.

**Impact of GH Treatment on Self-Esteem and Quality of Life in Children With Idiopathic
Short Stature**

Advocates of GH therapy often cite the potential psychosocial impairments associated with short
stature. Several RCTs have addressed this topic, and they have not found better self-esteem,
psychological functioning, or quality of life in children treated with GH compared with controls.
These studies are briefly described next.

In 2004, Ross et al published findings on psychological adaptation in 68 children with idiopathic
short stature without GHD.52 Children (mean age, 12.4 years) were randomized to receive GH
therapy (n=37) or placebo (n=31) 3 times per week until height velocity decreased to less than
1.5 cm/y. At baseline and then yearly, parents and children completed several psychological
instruments including the Child Behavior Checklist (CBCL) and Self-Perception Profile (SPP).
No significant associations were found between attained height SDS or change in height SDS
and annual changes in scores on the CBCL. There were no significant differences between
groups on any CBCL summary scales in years 1 and 2, but, in year 4, there were significantly
higher scores on the CBCL summary scales in the group receiving GH treatment. There were no
significant differences between groups on the SPP at any follow-up point. In conclusion, short
stature in this study was not associated with problems in psychological adaptation or self-
concept.

Theunissen et al in the Netherlands published a trial in 2002 in which 40 prepubertal children
with idiopathic short stature were randomly assigned to GH treatment (n=20) or a control group
(n=20).53 Parents and children were interviewed at baseline and at 1 and 2 years to obtain
information on health-related quality of life (HRQOL) and children’s self-esteem. At the 2-year
follow-up, satisfaction with current height was significantly associated with improvement in
children’s reported HRQOL, social functioning, and other psychosocial measures. However,
satisfaction with height did not differ significantly between the treatment and control groups. The
data from this study do not support the hypothesis that GH treatment improves HRQOL in
children with idiopathic short stature.

In 1996, Downie et al examined the behavior of children without documented GHD who were
treated with GH due to idiopathic short stature.54 Across measures of behavior, including IQ,
self-esteem, self-perception, or parental perceptions of competence, there were no significant
differences between the control and the treatment groups, either at baseline or after 5 years of
GH therapy. The authors concluded that while no psychosocial benefits of GH therapy have been
demonstrated, likewise, no documented psychosocial ill effects of GH treatment have been
demonstrated.

**Section Summary: Impact of GH Treatment on Self-Esteem and Quality of Life in Children
With Idiopathic Short Stature**
RCTs have not found that short stature is associated with psychological problems, in contrast to the expectations of some advocates. In addition, the available trials have not reported a correlation between increases in height and improvements in psychological functioning. Moreover, this group of children is otherwise healthy and there are potential risks to GH therapy in childhood (see previous section Safety of GH Treatment).

**GH Use in Children With “Genetic Potential” (ie, Lower Than Expected Height Percentiles Based on Parents’ Height)**

No randomized or nonrandomized studies were identified that evaluated the efficacy, safety, and/or psychosocial impacts of treating this group of children with GH therapy.

**GH Therapy in Conjunction With GnRH Therapy as a Treatment of Precocious Puberty**

Precocious puberty is generally defined as the onset of secondary sexual characteristics before 8 years of age in girls and 9 years in boys. Central precocious puberty is related to hypothalamic pituitary gonadal activation, leading to increase in sex steroid secretion, which accelerates growth and causes premature fusion of epiphyseal growth plates, thus impacting final height. Children with precocious puberty are often treated with GnRH analogs to suppress the pituitary gonadal activity, to slow the advancement of bone age, and to improve adult height. Several long-term studies have reported that treatment with GnRH analogs is associated with improved adult height in most cases, particularly in those with the most accelerated bone age progression at treatment onset, the shortest predicted height, and the greatest difference between the target height and the predicted height. In contrast, patients with a slowly progressive form in which the predicted height does not change after 2 years of follow-up may not require any treatment. In another subset of patients, GnRH analog therapy may be associated with a marked deceleration of bone growth that may ultimately result in an adult stature that is less than the targeted midparental height. GH may be offered to these patients to achieve the targeted adult height. There have been no RCTs comparing final adult height in those treated with GnRH analogs alone versus GnRH analogs combined with GH therapy, and the largest case series includes 35 patients. Case series suggest that GH is most commonly offered as an adjunct to GnRH analogs when the growth velocity drops below the 25th percentile for chronologic age. Several comparative case series reporting final adult heights have been published by the same group of investigators from Italy. This is the only group to have reported final adult heights. The most recent studies focus on a group of 17 girls with precocious puberty and a growth velocity below the 25th percentile who were treated with a combination of GnRH and GH, and 18 girls who refused treatment with adjunctive GH. Those in the combined group attained a significantly greater adult height (161.2±4.8 cm) than the “control” group (156.7±5.7 cm). This small study is inadequate to permit scientific conclusions. Tuvemo et al reported on the results of a trial that randomized 46 girls with precocious puberty to receive either GnRH analogs or GnRH analogs in addition to GH. Of interest, all participants were adopted from developing countries; precocious puberty is thought to be common in such cross-cultural adoptions. Criteria for participation in this trial did not include predicted adult height or growth velocity. After 2 years of treatment, mean growth and predicted adult height were greater in those receiving combined
treatment than in those receiving GnRH analogs alone. The absence of final height data limits interpretation of this trial.

**GH Therapy in Older Adults**
The GH secretion rate decreases by an estimated 14% per decade after young adulthood; mean levels in older adults are less than half those of a young adult. However, mean GH levels in older adults are greater than age-matched adults with diagnosed GHD. Older individuals experience changes in body composition, loss of muscle mass, and decreases in BMD that are similar to changes seen in adults with biochemically verified GHD. Based on these observations, GH therapy has been investigated in older adults without organic pituitary disease. The evaluation of this off-label application is based on a 2001 TEC Assessment, which concluded that there was insufficient evidence of efficacy. It is not possible to prove effectiveness of GH treatment or lack thereof unless otherwise similar groups of treated versus nontreated patients are compared over a sufficient length of time to allow detection of any significantly and clinically different results.

**GH Therapy for Cystic Fibrosis**
A 2013 Cochrane systematic review evaluated GH therapy for improving lung function, nutritional status, and quality of life in children and young adults with cystic fibrosis. The authors identified 4 RCTs with a total of 161 participants. All studies used daily subcutaneous injection of rhGH as the intervention and included a no treatment or placebo control group. All studies measured pulmonary function and nutritional status. However, due to differences in how these outcomes were measured, study findings were not pooled. Previously, a 2010 systematic review identified 10 controlled trials evaluating GH for treating patients with cystic fibrosis. One study was placebo-controlled, 8 compared GH therapy with no treatment, and the remaining trial compared GH alone with glutamine or glutamine plus GH. In 1 study, patients were treated with GH for 4 weeks and, in the other studies, duration of treatment ranged from 6 months to 1 year. There were insufficient data to determine the effect of GH on most health outcomes including frequency of intravenous antibiotic treatment, quality of life, and bone fracture. Data were pooled on 1 outcome, frequency of hospitalizations. In trials with durations of at least 1 year, there was a significantly lower rate of hospitalizations per year in the group receiving GH therapy (pooled effect size, -1.62; 95% CI, -1.98 to -1.26).

One of the RCTs was an industry-sponsored open-label study published by Stalvey et al in 2012. This study compared GH therapy with no treatment in prepubertal children with cystic fibrosis who were younger than 14 years old. The eligibility criteria included height no more than 10th percentile for age and sex; and children with documented GHD were excluded. Participants were treated daily for 12 months and followed for an additional 6 months. The study included 68 children; 62 (91%) were included in the efficacy analysis, and all but 1 were included in the safety analysis. Annualized height velocity at month 12 was 8.2 cm/y (SD=2.1) in the treatment group and 5.3 cm/y (SD=1.3) in the control group; the difference between groups was statistically significant (p<0.001). Mean height SDS in the treatment group was -1.8 at baseline, -1.4 at 12 months, and -1.4 at 18 months. Mean height SDS in the control group was -1.9 at all 3 time points. Change in mean height SDS from baseline to 12 months was significantly greater in the treatment than in the control group (p<0.001). Between months 12
and 18 (after treatment ended), the control group remained at the same height SDS, and the
treatment group experienced a slight decline (0.1 SDS), but maintained a 0.5 SDS advantage
over the control group.

In terms of pulmonary outcomes, the unadjusted rate of change from baseline to 12 months in
most variables (7/8 pulmonary test results) did not differ between groups. However, the
unadjusted change from 12 to 18 months (after treatment ended) was significantly greater in the
control group than the treatment group in 4 of 7 pulmonary test variables, including forced
expiratory volume in 1 second (FEV₁) (p<0.005) and forced vital capacity (p<0.01). In the
treatment group, mean FEV₁ was 1209 L (SD=451) at baseline, 1434 L (SD=539) at 12 months,
and 1467 L (SD=568) at 18 months. This compared with 1400 L (SD=495) at baseline, 1542 L
(SD=510) at 12 months, and 1674 L (SD=510) at 18 months in the control group. From baseline
to 12 months, the between-group difference in change in the 6-minute walk distance was 26.3
meters (95% CI, -44.8 to 97.4; p=0.46). Ten children in the treatment group and 9 in the control
group were hospitalized for pulmonary exacerbations during the 12-month study period; the
difference between groups was not statistically significant. In general, treatment with GH
resulted in statistically significant improvement in height SDS but did not significantly improve
outcomes associated with cystic fibrosis. This study was not blinded; however, blinding was
less of a potential bias in this study because it had objective outcomes such as height and
hospitalization rate.

**Section Summary: Conditions Without GHD**
GH treatment has been used in numerous conditions where there is no documented GHD. For
some conditions associated with growth failure, such as Turner syndrome, Noonan syndrome,
SHOX mutations, short bowel syndrome, and children with renal insufficiency, there is FDA-
approval for GH treatment. Some clinical trial evidence indicates treatment leads to improved
growth velocity and/or final height, and there is support for use of GH in clinical practice
guidelines. The evidence is mixed on use of GH therapy for treating severe burns, with numerous
trials and systematic reviews reporting improved healing times. Some, but not all, controlled
studies have found improved clinical outcomes (eg, lower mortality, shorter hospital stay) when
GH therapy was used.

Some FDA-approved indications for GH treatment have no associated pathologic disorders.
They include pediatric patients born small for gestational age and children with height that is
more than 2.25 SD below the age-adjusted mean. For these situations, use of GH replacement
has not been demonstrated to have health outcome benefits other than improved height, and there
is the potential for AEs. For numerous other indications not FDA-approved, there is a variable
amount of evidence on the impact of GH replacement on height, but there is a lack of evidence
establishing that outcomes other than height are improved.

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 2.
**Summary of Evidence**

The evidence for growth hormone (GH) therapy in individuals with short stature due to proven growth hormone deficiency (GHD), Turner syndrome, Prader-Willi syndrome, Noonan syndrome, SHOX (short stature homeobox-containing gene) deficiency, or children with height below the 3rd percentile for chronologic age with chronic renal insufficiency includes randomized controlled trials (RCTs). Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. Studies have shown that GH therapy can improve growth velocity and final height and, in some cases, improve other outcomes such as motor development. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for GH therapy in individuals with AIDS wasting includes a systematic review of controlled and uncontrolled studies. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. The available studies found significant improvement in lean body mass with GH therapy and several found improvements in quality of life. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for GH therapy in individuals with burns includes RCTs and a Cochrane systematic review. Relevant outcomes are symptoms, hospitalizations, and treatment-related morbidity. Pooled analyses found significantly shorter healing time and significantly shorter hospital stays with GH therapy versus placebo. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for GH therapy in individuals with short bowel syndrome includes RCTs and a Cochrane systematic review. Relevant outcomes are functional outcomes, health status measures, and treatment-related morbidity. A pooled analysis of 3 small trials found a significantly greater weight gain with GH therapy compared with placebo and others studies have found improved intestinal absorption on patients with short bowel syndrome receiving parenteral nutrition. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for GH therapy in individuals with other conditions not associated with proven growth hormone deficiency or specific genetic syndromes includes controlled and uncontrolled studies. Relevant outcomes are functional outcomes, health status measures, quality of life, and
treatment-related morbidity. Whereas some studies have shown improvement in growth or height, there is insufficient evidence for any of these conditions that GH therapy improves functional or psychological outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Pediatric Endocrine Society
In 2015, the Pediatric Endocrine Society Drug and Therapeutics Committee published an evidence-based report on risk of neoplasia in patients receiving GH therapy. The report concluded that GH therapy can be administered without concerns about impact on neoplasia in children without known risk factors for malignancy. For children with medical conditions associated with an increased risk of future malignancies, cases should be evaluated on an individual basis and decisions made about the tradeoff between a possible benefit of GH therapy and possible risks of neoplasm.

Growth Hormone Research Society
In 2013, a Growth Hormone Research Society workshop issued consensus guidelines on recombinant human growth hormone (rhGH) therapy in Prader-Willi syndrome (PWS). The following were among the group’s recommendations:

- “After genetic confirmation of the diagnosis of PWS, rhGH treatment should be considered and, if initiated, should be continued for as long as demonstrated benefits outweigh the risks.”
- “GH stimulation testing should not be required as part of the therapeutic decision-making process in infants and children with PWS.”
- “Exclusion criteria for starting rhGH in patients with PWS include severe obesity, uncontrolled diabetes, untreated severe obstructive sleep apnea, active cancer, and active psychosis.”
- Scoliosis and cognitive impairment should not be considered exclusion criteria.

Endocrine Society
An Endocrine Society clinical practice guideline on adult growth hormone deficiency (GHD), updated in 2011, includes the following statements:

- The Task Force recommends that GH therapy of GH-deficient adults offers significant clinical benefits in body composition and exercise capacity.
- The Task Force suggests that GH therapy of GH-deficient adults offers significant clinical benefits in skeletal integrity.
- The Task Force recommends after documentation of persistent GHD that GH therapy be continued after completion of adult height to obtain full skeletal/muscle maturation during the transition period.
National Institute of Health and Clinical Excellence
In 2010, the National Institute of Health and Clinical Excellence (NICE) in the U.K. issued guidance on rhGH for growth failure in children. NICE recommends GH as a possible treatment for children with growth failure who have any of the following conditions:

- Growth hormone deficiency
- Turner syndrome
- Prader-Willi syndrome
- Chronic renal insufficiency
- Small for gestational age and have growth failure at 4 years
- Short stature homeobox (SHOX) gene deficiency

American Association of Clinical Endocrinologists
In 2009, the American Association of Clinical Endocrinologists issued updated guidelines on GH use in GH-deficient adults and transition patients. Evidence-based recommendations include the following:

- Growth hormone deficiency (GHD) is a well-recognized clinical syndrome in adults that is associated with significant comorbidities if untreated
- Growth hormone (GH) should only be prescribed to patients with clinical features suggestive of adult growth hormone deficiency and biochemically proven evidence of adult growth hormone deficiency
- No data are available to suggest that GH has beneficial effects in treating aging and age-related conditions and the enhancement of sporting performance; therefore, the guideline developers do not recommend the prescription of GH to patients for any reason other than the well-defined approved uses of the drug.

Growth Hormone Research Society et al
In 2008, the Growth Hormone Research Society, Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop published a consensus statement on the diagnosis and treatment of children with idiopathic short stature. Within the working group that developed the statement, the appropriate height below which GH treatment should be considered ranged from -2 to -3 SDS. The optimal age for treatment was thought to be between 5 years and early puberty. The group noted that psychological issues should be considered, eg, GH therapy should not be recommended for short children who are unconcerned about stature.

American Academy of Pediatrics
In January 1997, the American Academy of Pediatrics published a document that recommended the following patient selection criterion for children with short stature not associated with classic GH deficiency:
“Therapy with GH is medically and ethically acceptable in patients whose extreme short stature keeps them from participating in basic activities of daily living and who have a condition for which the efficacy of GH therapy has been demonstrated.”

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

V. DEFINITIONS

GROWTH HORMONE is a hormone secreted by the anterior pituitary that regulates cell division and protein synthesis necessary for normal growth.

OFF-LABEL refers to the use of a drug to treat a condition for which it has not been approved by the U.S. Food and Drug Administration (FDA), especially when such may relieve unpleasant symptoms or prove compassionate. Drug effects that have been observed but not specifically proven (and for which no application has been made) may be utilized for unproven or “off-label” uses by licensed medical practitioners.

RECOMBINANT refers to genetic material from different sources.

SOMATOTROPHIC refers to influencing the body or body cells.

SUBCUTANEOUS refers to beneath the skin.

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member’s contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER
Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

**Covered when medically necessary:**

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J2940</td>
<td>Injection, somatrem, 1 mg</td>
</tr>
<tr>
<td>J2941</td>
<td>Injection, somatropin, 1 mg</td>
</tr>
<tr>
<td>S9558</td>
<td>Hit growth hormone w/care coordination per diem</td>
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<table>
<thead>
<tr>
<th>ICD-10-CM Diagnosis Code*</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>B20</td>
<td>Human immunodeficiency virus [HIV] disease</td>
</tr>
<tr>
<td>E23.0</td>
<td>Hypopituitarism</td>
</tr>
<tr>
<td>E78.72</td>
<td>Smith-Lemli-Opitz syndrome</td>
</tr>
<tr>
<td>K91.2</td>
<td>Postsurgical malabsorption, not elsewhere classified</td>
</tr>
<tr>
<td>K91.2</td>
<td>Postsurgical malabsorption, not elsewhere classified</td>
</tr>
<tr>
<td>N25.0</td>
<td>Renal osteodystrophy</td>
</tr>
<tr>
<td>Q55.4</td>
<td>Other congenital malformations of vas deferens, epididymis, seminal vesicles and prostate</td>
</tr>
<tr>
<td>Q87.1</td>
<td>Congenital malformation syndromes predominantly associated with short stature</td>
</tr>
<tr>
<td>Q87.2</td>
<td>Congenital malformation syndromes predominantly involving limbs</td>
</tr>
<tr>
<td>Q87.3</td>
<td>Congenital malformation syndromes involving early overgrowth</td>
</tr>
<tr>
<td>Q87.81</td>
<td>Alport syndrome</td>
</tr>
<tr>
<td>Q96.0</td>
<td>Karyotype 45, X</td>
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<tr>
<td>Q96.1</td>
<td>Karyotype 46, X iso (Xq)</td>
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<tr>
<td>Q96.2</td>
<td>Karyotype 46, X with abnormal sex chromosome, except iso (Xq)</td>
</tr>
<tr>
<td>ICD-10-CM Diagnosis Code*</td>
<td>Description</td>
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<td>--------------------------</td>
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<tr>
<td>Q96.3</td>
<td>Mosaicism, 45, X/46, XX or XY</td>
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<tr>
<td>Q96.4</td>
<td>Mosaicism, 45, X/other cell line(s) with abnormal sex chromosome</td>
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<tr>
<td>Q96.8</td>
<td>Other variants of Turner’s syndrome</td>
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<td>Q96.9</td>
<td>Turner’s syndrome, unspecified</td>
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<td>T20.30XA</td>
<td>Burn of third degree of head, face, and neck, unspecified site, initial encounter</td>
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<tr>
<td>T20.70XA</td>
<td>Corrosion of third degree of head, face, and neck, unspecified site, initial encounter</td>
</tr>
<tr>
<td>T21.30XA</td>
<td>Burn of third degree of trunk, unspecified site, initial encounter</td>
</tr>
<tr>
<td>T21.70XA</td>
<td>Corrosion of third degree of trunk, unspecified site, initial encounter</td>
</tr>
<tr>
<td>T22.30XA</td>
<td>Burn of third degree of shoulder and upper limb, except wrist and hand, unspecified site, initial encounter</td>
</tr>
<tr>
<td>T22.70XA</td>
<td>Corrosion of third degree of shoulder and upper limb, except wrist and hand, unspecified site, initial encounter</td>
</tr>
<tr>
<td>T23.301A</td>
<td>Burn of third degree of right hand, unspecified site, initial encounter</td>
</tr>
<tr>
<td>T23.302A</td>
<td>Burn of third degree of left hand, unspecified site, initial encounter</td>
</tr>
<tr>
<td>T23.309A</td>
<td>Burn of third degree of unspecified hand, unspecified site, initial encounter</td>
</tr>
<tr>
<td>T23.701A</td>
<td>Corrosion of third degree of right hand, unspecified site, initial encounter</td>
</tr>
<tr>
<td>T23.702A</td>
<td>Corrosion of third degree of left hand, unspecified</td>
</tr>
<tr>
<td>T23.709A</td>
<td>Corrosion of third degree of unspecified hand, unspecified site, initial encounter</td>
</tr>
<tr>
<td>T24.301A</td>
<td>Burn of third degree of unspecified site of right lower limb, except ankle and foot, initial encounter</td>
</tr>
<tr>
<td>T24.302A</td>
<td>Burn of third degree of unspecified site of left lower limb, except ankle and foot, initial encounter</td>
</tr>
<tr>
<td>T24.309A</td>
<td>Burn of third degree of unspecified lower limb, except ankle and foot, initial encounter</td>
</tr>
<tr>
<td>T24.701A</td>
<td>Corrosion of third degree of unspecified site of right lower limb, except ankle and foot, initial encounter</td>
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<tr>
<td>T24.702A</td>
<td>Corrosion of third degree of unspecified site of left lower limb, except ankle and foot, initial encounter</td>
</tr>
<tr>
<td>T24.709A</td>
<td>Corrosion of third degree of unspecified lower limb, except ankle and foot, initial encounter</td>
</tr>
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<td>T30.0</td>
<td>Burn of unspecified body region, unspecified degree</td>
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<td>T30.0</td>
<td>Burn of unspecified body region, unspecified degree</td>
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<tr>
<td>T30.4</td>
<td>Corrosion of unspecified body region, unspecified degree</td>
</tr>
</tbody>
</table>

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses
IX. REFERENCES


50. Deodati A, Cianfarani S. Impact of growth hormone therapy on adult height of with idiopathic short stature: systematic review. BMJ. 2011;342:c7157. PMID 21398350
hormone-deficient adults and transition patients – 2009 update.  


Other:

The Centers for Medicare & Medicaid Services (CMS), Medicare Benefit Policy Manual, 100-2, Chapter 15, Section 50.4.2, Unlabeled Use of Drugs


X. POLICY HISTORY

<table>
<thead>
<tr>
<th>MP 2.109</th>
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<td>CAC 9/28/10 Consensus Review</td>
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<td></td>
<td>CAC 10/25/11 Consensus Review</td>
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</table>
|          | CAC 8/28/12 Adopt BCBSA with exception of retaining treatment of pediatric patients (<5 years of age) born small for gestational age and who failed to show catch-up growth by age two and were two standard deviations below the mean as medically necessary, Additional criteria for evaluation for OSA and treatment if indicated has been added to the GH indication for Prader-Willi syndrome. Short stature after renal transplantation as an investigational indication has been removed. Treatment of children with “genetic potential “(i.e., lower than expected height percentiles based on parents` height) has been added as investigational. Policy guidelines have been added which further define medically necessary indications. Criteria for diagnostic testing for GH deficiency utilizing twenty-four (24) hour continuous monitoring of GH hormone levels and serum levels of insulin-like
growth factors (IGF) or insulin-like growth factor binding protein (IGFPB) have been removed from the policy. FEP variation revised.
Codes reviewed 8/13/12 klr

**CAC 7/30/13** Consensus review. References updated. Children with short stature due to SHOX (short stature homeobox-containing gene) deficiency added to list of medically necessary indications however this was already listed in the table as an FDA-approved indication for Humatrope. ‘Patients’ with growth failure due to Prader-Willi syndrome changed to ‘children’ with growth failure due to Prader-Willi syndrome. Administrative code review complete.

**CAC 3/25/14** Consensus review. References updated. No changes to the policy statements. Rationale added. Medicare variation removed FEP variation revised to reflect new policy numbers. Codes reviewed.

**CAC 3/24/15** Consensus. No change to policy statements. References and rationale updated. Policy Coded.


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**TOP**