Title: Human Growth Hormone

Pre-Determination of Services IS REQUIRED by the Member's Contract

Prior Authorization Form:
BCBSKS will review Prior Authorization requests

Link to Drug List (Formulary):
http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list.shtml

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<td>Original Effective Date: February 4, 1986</td>
<td>Original Effective Date: August 18, 2008</td>
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<td>Revision Date(s): January 30, 2014; December 9, 2014; J une 23, 2015; December 8, 2015; January 1, 2017; May 24, 2017; August 18, 2017</td>
<td>Revision Date(s): January 30, 2014; December 9, 2014; June 23, 2015; December 8, 2015; January 1, 2017; May 24, 2017; August 18, 2017</td>
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<td>Current Effective Date: August 18, 2017</td>
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State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member’s benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

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<td>• With altered body habitus related to antiretroviral therapy for HIV infection</td>
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<tr>
<td>• With &quot;genetic potential&quot; (ie, lower than expected height percentiles based on parents' height)</td>
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<td>• Functional outcomes</td>
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<td>• Treatment-related morbidity</td>
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</tbody>
</table>

*Contains Public Information*
Populations | Interventions | Comparators | Outcomes
---|---|---|---
Individuals:  
• Who are older adults with age-related growth hormone deficiency  
Interventions of interest are:  
• Human growth hormone  
Comparators of interest are:  
• Standard care without human growth hormone treatment  
Relevant outcomes include:  
• Functional outcomes  
• Quality of life  
• Treatment-related morbidity
Individuals:  
• With cystic fibrosis  
Interventions of interest are:  
• Human growth hormone  
Comparators of interest are:  
• Standard care without human growth hormone treatment  
Relevant outcomes include:  
• Functional outcomes  
• Quality of life  
• Treatment-related morbidity

**DESCRIPTION**
Recombinant human growth hormone (GH) is approved by the U.S. Food and Drug Administration for various indications and is also proposed for various nonlabeled indications, such as cystic fibrosis and treatment of older adults without documented growth hormone deficiency (GHD).

**OBJECTIVE**
The objective of this evidence review is to evaluate the net health outcome when human growth hormone is used to treat various Food and Drug Administration-approved and off-label indications compared with the net health outcome achieved by standard therapy for that condition.

**BACKGROUND**
Human growth hormone (GH), also known as somatotropin, is synthesized in somatotropic cells of the anterior lobe of the pituitary gland. Growth hormone deficiency (GHD) can occur for various 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. They include changes in body composition, higher levels of low-density lipoprotein cholesterol, lower bone density, and a decreased self-reported quality of life compared with healthy peers. Some evidence suggests that there may be increases in cardiovascular disease and overall mortality, but it is less clear whether GHD is causative for these outcomes.

Beginning in 1985, recombinant human growth hormone (rhGH) has been marketed for a variety of Food and Drug Administration (FDA)–labeled indications.

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, somatropin (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 retardation. 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.

Outcome Measures in GH Research
The most common outcome measure reported in GH research is change in height. For some situations, such as in patients with documented 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 insufficient evidence to establish that short stature is associated with substantial impairments in psychological functioning or quality of life, or that increases in height improve these parameters. Similarly, improvements in other measures of body composition (eg, muscle mass, 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 outcomes measures (eg, functional status,
quality of life, disease-specific clinical outcomes) are necessary to demonstrate an improvement in health outcomes.

The intent of the Growth Hormone Prior Authorization (PA) Criteria is to appropriately select patients for therapy according to Food and Drug Administration (FDA) approved product labeling and/or clinical guidelines and/or clinical studies. When criteria for use are met, the preferred agent may be approved for use; use of the nonpreferred growth hormone products will be evaluated if the prescriber indicates a history of a trial of, documented intolerance of, FDA labeled contraindication to, or hypersensitivity to the preferred growth hormone.

### TARGET DRUGS

<table>
<thead>
<tr>
<th>Preferred Growth Hormone</th>
<th>Nonpreferred Growth Hormone</th>
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<tbody>
<tr>
<td>• Omnitrope®</td>
<td>• Genotropin®</td>
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<td>• Humatrope®</td>
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<td>• Norditropin® NordiFlex,</td>
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<td>Norditropin Flexpro</td>
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<td>• Nutropin®</td>
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<td>• Nutropin AQ®</td>
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<td>• Nutropin AQ Nuspin®</td>
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<td>• Saizen®, Saizen Click.Easy</td>
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<td>• Serostim®</td>
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<td>• Zorbtive®</td>
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A **nonpreferred Growth Hormone** will be approved when ONE of the following is met:

1. The patient's medication history indicates use of the *preferred* growth hormone (GH) agent **OR**
2. The patient has documented intolerance, FDA labeled contraindication, or hypersensitivity to the *preferred* GH agent.

### POLICY

**A. Pediatric Growth Hormone Therapy**

Growth hormone therapy is contractually excluded for those under age 18, except for the following specific conditions:

1. **Growth Hormone Deficiency or Insufficiency** as defined by:
   
   a. Insulin tolerance test with documented hypoglycemia (blood sugars less than 40 mg/dL) and peak GH value of <10 ng/mL.

   **OR**
At least two provocative stimulation tests using arginine, clonidine, glucagon, growth hormone releasing hormone (GHRH), or levodopa with peak GH values <10 ng/mL on all tests.

AND

b. Growth failure as defined by the following age groups:
   - 0-6 months: <34 cm/year
   - 6-12 months: <15 cm/year
   - 1-3 years: <12 cm/year
   - Over three years to puberty (see definition of puberty below): <5 cm/year
   - Puberty (defined as bone age of 10½ - 12 years for girls and bone age of 12½ - 14½ years for boys): <6 cm/year

Note: Growth rates should be tracked over at least one year. Continuation of treatment with growth hormone therapy requires a growth rate above 2.5 cm/year.

2. Panhypopituitarism subject to meeting all of the following criteria:
   a. Deficiencies of 3 or more other pituitary hormones (TSH, ACTH, FSH/LH, antidiuretic hormone)
   b. Low IFG-1 concentration

Note: Growth hormone stimulation testing is not required in these cases. Growth hormone therapy may be approved for life.

3. Turner, Prader-Willi, and Noonan Syndromes With Growth Failure subject to meeting all of the following criteria:
   a. Height less than the 2.5 percentile for age and sex
   b. Growth failure as defined by the following age groups:
      - 0-6 months: <34 cm/year
      - 6-12 months: <15 cm/year
      - 1 - 3 years: <12 cm/year
      - Over three years to puberty (see below definition of puberty): <5 cm/year
      - Puberty (defined as bone age of 10½ - 12 years for girls and bone age of 12½ - 14½ years for boys): <6 cm/year

Note: Growth rates should be tracked over at least one year (except age groups < 1 year). Growth hormone stimulation testing is not required in these cases.
4. Chronic Renal Insufficiency or End Stage Renal Disease as defined by:
   a. Chronic renal insufficiency defined as GFR less than 60 mL/min/1.73m² prior to successful transplant
   b. End stage renal disease defined as serum creatinine greater than 1.5 mg/dL or GFR less than 75 mL/min/1.73m² prior to successful transplant
   c. With open epiphyses
   d. Height less than the 2.5 percentile for age and sex
   e. Growth failure as defined by the following age groups:
      • 0-6 months: <34 cm/year
      • 6-12 months: <15 cm/year
      • 1 - 3 years: <12 cm/year
      • Over three years to puberty (see below definition of puberty): <5 cm/year
      • Puberty (defined as bone age of 10½ -12 years for girls and bone age of 12½ -14½ years for boys): <6 cm/year
   f. Complicating factors have been treated including malnutrition and acidosis

   Note: Growth rates should be tracked over at least one year (except age groups < 1 year).
   Growth Hormone stimulation testing is not required.
   Growth Hormone is discontinued at the time of transplantation or other conditions below for termination of GH therapy.

5. Neonate (≤4 months of age) with hypoglycemia in the absence of metabolic disorder AND growth hormone level is <20 ng/mL.

6. AIDS wasting.


8. Short bowel syndrome receiving specialized nutritional support in conjunction with optimal management of short bowel syndrome (see Policy Guidelines).
**Termination of Growth Hormone Therapy**

Growth hormone therapy is **not medically necessary** when any one of the following criteria is met:

1. Epiphyseal fusion has occurred.
2. Mid-parental height is achieved. Mid-parental height = (father’s height + mother’s height) divided by 2, plus 2.5 inches (6.4 cm) (male) or minus 2.5 inches (6.4 cm) (female).
3. Failure to respond to growth hormone therapy with a growth rate of less than 2.5 cm/year.

**Documentation**

Documentation needed for predetermination is:
- Growth charts with at least 3 measurements over at least one year
- Growth hormone stimulation testing results
- Other supporting documentation

**Length of Approval:** Growth hormone therapy approved for life (e.g., panhypopituitarism, or when adult GH therapy requirements are met) will need continued review for benefits.

**B. Adult Growth Hormone Therapy**

1. Growth hormone therapy is excluded for those over the age of 18 with the following exceptions:
   a. Hypothalamic or pituitary disease or injury and laboratory proven growth hormone deficiency by GH stimulation testing.
   b. Childhood onset of growth hormone deficiency and deficiency is demonstrated by GH stimulation retesting during adulthood
   c. Panhypopituitarism with deficiencies of 3 or more other pituitary hormones (TSH, ACTH, FSH/LH, antidiuretic hormone) and low values for IGF-1

2. Growth hormone stimulation for GH deficiency must be documented by the following criteria:
   a. Insulin tolerance test with documented hypoglycemia (blood sugars less than 40 mg/dL) and peak growth hormone values < 5ng/mL, OR
   b. Arginine-GHRH stimulation test (peak growth hormone values <4.1ng/mL)
OR

c. Arginine L-Dopa stimulation test (peak growth hormone values <1.5ng/mL)

OR

d. Glucagon stimulation test (peak growth hormone values <3ng/mL)

OR

e. A below normal level of IGF-1 when associated with panhypopituitarism with documented multiple hormone deficiencies (3 or more deficiencies: TSH, ACTH, FSH/LH, antidiuretic hormone) as a result of pituitary or hypothalamic disease secondary to tumor, surgery, inflammation, radiation therapy, severe head trauma or structural abnormality (septo-optic dysplasia, ectopic neurohypophysis). Growth hormone stimulation testing is not necessary in these cases.

3. Continuation of approval for growth hormone therapy requires some indication of a clinical response to the growth hormone during the first 12 months of therapy: weight loss, improvement on lipid profile, increased bone mass, increased muscle strength or increase of IGF-1 into the normal range. Children on GH therapy who continue growth GH therapy into adulthood or adults with hypopituitarism of recent onset will not exhibit the manifestations of adult GH deficiency and will not show the improvements listed above.

4. AIDS wasting.

5. Promotion of wound healing in patients with severe burns (see Policy Guidelines).

6. Short bowel syndrome receiving specialized nutritional support in conjunction with optimal management of short bowel syndrome (see Policy Guidelines).

Length of Approval: 12 months

Growth hormone therapy approved for life will need continued review for benefits.

Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Policy Guidelines
1. 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.

2. The FDA cautions that the safety and effectiveness of GH therapy in adults aged 65 and older 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.

3. Growth hormone is contraindicated in patients with Prader-Willi syndrome, who are severely obese or who have severe respiratory impairment. Sleep studies are recommended prior to initiation of growth hormone therapy for obese pediatric patients with Prader-Willi syndrome.

4. Insulin tolerance testing is contraindicated in patients with cardiovascular disease, cerebrovascular disease, seizure disorders or patients older than 65 years.

5. AIDS wasting is defined as a weight loss of more than 10% of baseline that cannot be explained by a concurrent illness other than HIV infection. Patients treated with growth hormone must simultaneously be treated with antiviral agents. Therapy is continued until this definition is no longer met.

6. Growth hormone for burn patients should be limited to those patients with third-degree burns.

7. 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.

8. Member Contract Language:
   Growth Hormone therapy is covered only under one of the following circumstances:
   If under age 18 and diagnosed with:
   a. Both laboratory proven growth hormone deficiency or insufficiency and significant growth retardation; or
   b. Substantiated Turner's syndrome, Prader-Willi syndrome, or Noonan's syndrome with significant growth retardation; or
   c. Chronic renal insufficiency and end stage renal disease with significant growth retardation prior to successful transplantation; or
   d. Panhypopituitarism; or
   e. Neonatal hypoglycemia related to growth hormone deficiency.

   If age 18 and over with:
   a. Evidence of pituitary or hypothalamic disease or injury and laboratory proven growth hormone deficiency; or
   b. A history of prior growth hormone therapy for growth hormone deficiency or insufficiency in childhood and laboratory confirmation of continued growth hormone deficiency.
Children, Adolescents and Adults:
  a. AIDS wasting syndrome
  b. Short bowel syndrome
  c. Severe burn patients

**RATIONALE**

The policy was updated with a literature review using MEDLINE; most recently through August 18, 2016.

**Safety of Growth Hormone Treatment**

Adverse effects (AEs) can occur with growth hormone (GH) treatment. In children, increased rates of skeletal problems (eg, 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 also concern that GH treatment may increase the rate of malignancy, particularly de novo leukemia, in patients without risk factors. However, to date, there is insufficient evidence of a causative relation between GH treatment and malignancy rates.

Several publications on the safety of GH therapy have used French registry data and vital statistics. A 2012 analysis of long-term mortality after GH treatment was conducted by Carel et al.\(^3\) A total of 6928 children were included in the study. Indications for GH therapy included idiopathic isolated growth hormone deficiency (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 (1.42%) of the 6558 individuals 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% confidence interval [CI], 1.08 to 1.64). 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.\(^4\) 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 all of the 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.
According to the drug prescribing information, GH therapy use has been associated with sudden death in children with Prader-Willi syndrome. These deaths occurred among children who were severely obese or had severe respiratory impairment; these markers are now considered contraindications to GH treatment use.

**Growth Hormone Deficiency**

**GHD in Children**

In children with GHD, treatment has been found to increase 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 randomized controlled trials (RCTs) has shown 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 these findings were not robust 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 inconsistent and insufficient to determine whether these outcomes are improved with treatment.

**Section Summary: Growth Hormone Deficiency**

Large cohort studies, RCTs, and meta-analyses have found that, for patients with documented GHD and clinical manifestations such as short stature, GH replacement has improved growth velocity and final height achieved. In addition, studies have shown that GH therapy can ameliorate the secondary manifestations of GHD such as increase in lean muscle mass and BMD seen primarily in older children and adults.

**Short Stature Due to Prader-Willi Syndrome**

Most children with Prader-Willi syndrome have hypothalamic dysfunction and are GH-deficient. 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 improvements in health outcomes with GH treatment. For example, a 2008 RCT published by Festen et al included 42 infants and 49 prepubertal children.
(age range, 3-14 years). GHD status was not part of the study eligibility criteria. The study 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, 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 2-year, single-blind trial included 22 children newly diagnosed with Prader-Willi syndrome (mean age, 12.9 months). GHD status was not considered in the study eligibility criteria. 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 a finding that GH had statistically significant interaction effects for a model predicting motor development age using the Alberta Infant Motor Scale.

Lo et al (2015) conducted a 2-year RCT of GH therapy versus no treatment and followed children on GH therapy for an additional 6 years. The trial included 42 prepubertal children (age range, 3.5-14 years); children were not selected based on GHD status. The primary outcome was the impact of GH treatment on behavior, measured by 2 validated parent questionnaires: the Developmental Behavior Checklist (DBC) and the Children’s Social Behavior Questionnaire (CSBQ). At the end of the 2-year RCT, there were no significant differences in DBC and CSBQ scores between the GH-treated and no-treatment groups. Findings were similar at the end of the 8-year follow-up period.

**Section Summary: Short Stature due to Prader-Willi Syndrome**
Several RCTs have found improvement in height and other outcomes (eg, motor development) in children with Prader-Willi syndrome. One study did not find a significant change in problem behavior after GH treatment. Studies have found increased risk of adverse events in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment and thus these are contraindications.

**Short Stature Due to 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 ages 0 to 18 years. Five trials (total N=401 participants) met reviewers’ 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 mean difference (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 had to compare GH treatment with placebo, no treatment, or a different GH regimen, and needed to include height outcomes. Seven
RCTs with 809 children met reviewers’ criteria. Study entry criteria varied (eg, ranging from <3rd percentile for chronologic age to <50th percentile for chronologic 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 cm/y).

An example of an individual RCT is Hokken-Koelega et al, conducted in the Netherlands. This double-blind, placebo-controlled crossover trial included 20 prepubertal children with severe growth retardation and chronic renal failure. Entry criteria included height velocity less than the 25% percentile for chronologic 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 significantly affect parathyroid hormone concentrations, and there were no radiologic signs of renal osteodystrophy.

Section Summary: Short Stature due to Chronic Renal Insufficiency
Numerous RCTs and systematic reviews of these RCTs have found significantly increased height and height velocity in children with short stature associated with chronic renal insufficiency who were treated with GH therapy compared with another intervention. There were no significant increases in adverse events related to renal function.

Short Stature Due to Turner Syndrome
Short stature is almost universal in Turner syndrome, although the syndrome is not associated with GHD. 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). 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 patients) evaluating GH for treating Turner syndrome. Studies included children who had not yet achieved final height, had 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).

Section Summary: Short Stature due to Turner Syndrome
Several RCTs have been published and/or are reported in FDA documents. Studies have found that GH therapy increases height outcomes (eg, final height, height velocity) in children with short stature due to Turner syndrome compared with placebo or no treatment.
Short Stature Due to Noonan Syndrome

Noonan syndrome is associated with slow growth, starting in early childhood. In 2015, Giacomozzi et al published a systematic review of literature on the effect of GH therapy on adult height.27 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. Twenty-three studies met the inclusion criteria; none were RCTs and only 1 was controlled. Three studies were case reports and the remainder prospective or retrospective cohort studies. In the 1 controlled study (MacFarlane et al28), 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 were limited by the paucity of controlled studies and lack of RCTs.

Section Summary: Short Stature due to Noonan Syndrome

There are a number of studies; however, few included comparator interventions. A systematic review of the literature found that GH therapy was associated with an increase in height in patients with short stature due to Noonan syndrome.

Short Stature due to Short Stature Homeobox-Containing Gene Deficiency

A 2010 Health Technology Assessment on GH treatment of growth disorders in children identified 1 RCT evaluating GH therapy for children with short stature due to short stature homeobox-containing gene deficiency (SHOX).29 This industry-sponsored, open-label multicenter trial was published by Blum et al in 2007.30 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 usual care 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 usual care group (p<0.001). No serious adverse events were reported for either group.

Section Summary: Short Stature due to Short Stature Homeobox-Containing Gene Deficiency

An RCT found that children with short stature due to SHOX deficiency had significantly greater height velocity and significantly more height gain after 2 years when treated with GH versus no GH treatment.

Severe Burns

Treatment of Severe Burns

A 2012 Cochrane systematic review included RCTs evaluating the impact of GH therapy on the healing rates of burn wounds.31 Thirteen trials were identified that compared GH therapy with another intervention or to placebo. Six included only children and 7 involved only adults. Twelve 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 than in the placebo group (MD = -9.07 days; 95% CI, -4.39 to -13.76). The reviewers 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 treatment than in the control group (MD = -8.67 days; 95% CI, -5.95 to -11.39). The reviewers concluded that GH therapy may reduce the healing time for severe burns.
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 (relative risk [RR], 0.53; 95% CI, 0.22 to 1.29). The mortality analysis likely was underpowered; the total number of deaths was 17. A pooled analysis of 3 studies involving adults found significantly shorter hospital lengths of stay in patients who received GH therapy compared with placebo (MD = -12.55 days; 95% CI, -17.09 to -8.00 days). 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.32 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% for those 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%).33 Another placebo-controlled trial found no benefit to GH with regard to length of hospitalization in 24 adults with severe burns.34 These results are consistent with a 1996 TEC Assessment which evaluated the use of GH treatment for GH therapy for a variety of catabolic illnesses and found that, based on 6 trials, the use of GH treatment meets TEC criteria to improve wound healing in patients with 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.35 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.36

Section Summary: Severe Burns
Numerous RCTs evaluating GH for treatment of severe burns have been published. Pooled analyses found significantly shorter healing times and significantly shorter hospital stays with GH therapy versus placebo. Several RCTs have found significantly greater height gains in children with burns who received GH therapy versus placebo or no treatment.

AIDS Wasting
In 2004, Moyle et al published a systematic review of controlled and uncontrolled studies on selected treatments of HIV wasting.37 To be included, studies had 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 studies evaluating GH treatment found statistically significant improvements in some aspects of quality of life after 12 weeks. A 2005 double-blind RCT by Evans et al included 700 patients with HIV-associated wasting.38 Patients assigned to human GH had significantly greater increase in exercise capacity (the primary outcomes) than patients assigned to placebo.

Section Summary: AIDS Wasting
A systematic review of the literature found significant improvement in lean body mass with GH therapy versus placebo; several found improvements in quality of life. A subsequent RCT with a...
large sample size found a significantly greater increase in exercise capacity with GH treatment than with placebo.

**Short Bowel Syndrome with Specialized Nutritional Support**

Short bowel syndrome is experienced by patients who have had 50% or more of the small intestine removed. This procedure results in 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. Studies evaluated GH with or without glutamine treatment. The primary outcome was change in body weight. A pooled analysis of 3 small trials (n=30 patients) 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 kg; p<0.001).

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

**Section Summary: Short Bowel Syndrome With Specialized Nutritional Support**

A pooled analysis of 3 small RCTs 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.

**Small for Gestational Age Children**

A meta-analysis of RCTs evaluating GH treatment for children born small for gestational age was published in 2009. Four trials (total N=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 reviewers noted 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 retardation 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.
Section Summary: Small for Gestational Age Children
A meta-analysis found that GH treatment resulted in significantly greater adult height in SGA children than a control treatment. There are few data on psychological or functional outcomes associated with this additional gain in height.

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"). However, there is scant published literature on the use of GH for this indication. The literature is dominated by letters to 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. The authors reported improved waist/hip ratio and mid-thigh circumference.

Section Summary: Altered Body Habitus Related to Antiretroviral Therapy for HIV Infection
A single RCT reporting change in visceral abdominal fat provides insufficient evidence that GH treatment improves health outcomes in HIV-infected patients with altered body habitus related to antiretroviral therapy. Additional studies reporting a wider range of outcomes are needed.

Children with Idiopathic Short Stature (Without Documented GHD or Underlying Pathology)
Impact on Adult Height
Several meta-analyses have been published. Most recently, in 2011, Deodati and Cianfarani identified 3 RCTs and 7 non-RCTs. Selection criteria for the systematic review, 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. 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 RCT was placebo-controlled, and that trial had a high dropout rate (40% in the treated group, 65% in the placebo group).

In the 3 RCTs (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 2007, a Cochrane review by Bryant et al evaluated GH therapy for idiopathic short stature in children and adolescents. Ten RCTs met eligibility criteria, which included studies 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 had 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 significant 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.

Impact on Self-Esteem and Quality of Life

Advocates of GH therapy often cite the potential psychosocial impairments associated with short stature. Several RCTs have addressed this issue, and did not find 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.48 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. This study did not find a correlation between short stature and 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).49 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.50 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: 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.

RCTs have not found that short stature is associated with psychological problems, contrary 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 Growth Hormone Treatment).

Children with “Genetic Potential”
No randomized or nonrandomized studies were identified that have evaluated the efficacy, safety, and/or psychosocial impacts of treating children with “genetic potential” (ie, children with lower than expected high percentiles based on their parents’ height).

Treatment of Precocious Puberty in Conjunction with GnRH Therapy
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 analogues to suppress the pituitary gonadal activity, to slow the advancement of bone age, and to improve adult height.

One RCT compared GnRH analogues alone versus GnRH analogues combined with GH therapy. This trial, by Tuvemo et al, included 46 girls with precocious puberty. Criteria for participation 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 analogues alone. The absence of final height data limits interpretation of this trial.

In addition, a case series from Italy reported on 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 cm) than the “control” group (156.7 cm). This small study is inadequate to permit scientific conclusions.

Section Summary: Treatment of Precocious Puberty in Conjunction With GnRH Therapy
There are insufficient data on the incremental benefit of GH added to GnRH therapy in patients with precocious puberty. One RCT was published, but final height was not reported. One small comparative case series found significantly higher adult height with adjunctive GH therapy, but this study may have been subject to confounding. No studies have reported functional or psychological outcomes.

Older Adults with Age-Related Growth Hormone Deficiency
A 2001 TEC Assessment investigated the use of GH in older adults with age-related growth hormone deficiency and 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.
Section Summary: Older Adults
A TEC Assessment concluded that there is a lack of evidence that GH therapy in older adults improves health outcomes. No subsequent controlled studies were identified.

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 reviewers identified 4 RCTs (total N=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 others, durations 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 for 1 outcome, frequency of hospitalizations. In trials lasting at least 1 year, there were significantly lower rates of hospitalizations per year in groups 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. It compared GH therapy with no treatment in prepubertal children with cystic fibrosis who were younger than 14 years old. Eligibility criteria included height no more than the 10th percentile for age and sex; children with documented GHD were excluded. Participants were treated daily for 12 months and followed for another 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, while 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 in the treatment group for 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 liters (SD=451) at baseline, 1434 liters (SD=539) at 12 months, and 1467 liters (SD=568) at 18 months compared with 1400 liters (SD=495) at baseline, 1542 liters (SD=510) at 12 months, and 1674 liters (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 meters; 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.
treatment with GH resulted in statistically significant improvements in height SDS but did not significantly improve outcomes associated with cystic fibrosis.

Section Summary: Cystic Fibrosis
Several RCTs and systematic reviews have been published. The RCTs were heterogeneous and reported a variety of outcomes. One systematic review did not pool results for most outcomes, including frequency of intravenous antibiotic treatment, quality of life, and bone fracture. The pooled data on 1 outcome (hospitalizations) found significantly fewer hospitalizations in patients receiving GH therapy versus no treatment or placebo.

SUMMARY OF EVIDENCE
For individuals who have proven growth hormone deficiency (GHD) who receive human growth hormone (GH), the evidence includes randomized controlled trials (RCTs), large observational studies, and meta-analyses. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. Studies have found that, 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, studies have shown that GH therapy can ameliorate the secondary manifestations of GHD such as increase in lean muscle mass and bone mineral density seen primarily in older children and adults. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have short stature due to Prader-Willi syndrome who receive human GH, the evidence includes RCTs. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. Several RCTs have found improvement in height and other outcomes (eg, motor development) in children with Prader-Willi syndrome. Studies have found increased risk of adverse events in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment and thus GH is contraindicated. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have short stature due to chronic renal insufficiency who receive human GH, the evidence includes RCTs and systematic reviews. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. Systematic reviews of RCTs have found significantly increased height and height velocity in children with short stature associated with chronic renal insufficiency who are treated with GH therapy compared with other interventions. There were no significant increases in adverse events related to renal function. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have short stature due to Turner syndrome who receive human GH, the evidence includes RCTs. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. RCTs have found that GH therapy increases height outcomes (eg, final height, height velocity) in children with short stature due to Turner syndrome compared with placebo or no treatment. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have short stature due to Noonan syndrome who receive human GH, the evidence includes observational studies and a systematic review. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. There are a number of studies; however, few included treatment comparators. A systematic review found that GH therapy was associated with an increase in height in patients with Noonan syndrome. The
evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have short stature due to short stature homeobox-containing gene (SHOX) deficiency who receive human GH, the evidence includes an RCT and systematic review. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. An RCT found that children with short stature due to SHOX deficiency had significantly greater height velocity and height gain after 2 years when treated with GH versus no GH treatment. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have severe burns who receive human GH, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, hospitalizations, and treatment-related morbidity. Numerous RCTs evaluating GH for treatment of severe burns have been published. Pooled analyses have found significantly shorter healing times and significantly shorter hospital stays with GH therapy than with placebo. Several RCTs have found significantly greater height gain in children with burns who received GH therapy versus placebo or no treatment. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have AIDS wasting who receive human GH, the evidence includes observational studies, at least 1 RCT, and a systematic review. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. A systematic review found significant improvement in lean body mass with GH therapy versus placebo; several studies found improvements in quality of life. A subsequent RCT with a large sample size found a significantly greater increase in exercise capacity with GH than with placebo. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have short bowel syndrome on specialized nutritional support who receive human GH, the evidence includes RCTs and a meta-analysis. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. A pooled analysis of 3 small trials found significantly greater weight gain with GH therapy than with placebo and others studies found improved intestinal absorption on patients with short bowel syndrome receiving parenteral nutrition. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are small for gestational age (SGA) who receive human GH, the evidence includes RCTs and a meta-analysis. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. A meta-analysis found that GH treatment resulted in significantly greater adult height in SGA children than a control treatment. There are few data on the psychological or functional outcomes associated with this additional gain in height. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have altered body habitus related to antiretroviral therapy for HIV infection who receive human GH, the evidence includes case series. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. Case series data are insufficient for drawing conclusions about the impact of GH treatment on health outcomes in HIV-infected patients with altered body habitus related to antiretroviral therapy. Controlled studies reporting relevant outcomes are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.
For individuals who have idiopathic short stature who receive human GH, the evidence includes RCTs and systematic reviews. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. 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 available studies did not follow treated patients long enough to determine the ultimate impact of GH on final adult height. RCTs have not found that short stature is associated with psychological problems, contrary 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have “genetic potential” (ie, lower than expected height percentiles based on parents’ height) who receive human GH, the evidence includes no clinical trials. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. No published literature was identified on GH therapy as a treatment of children with “genetic potential.” The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have precocious puberty who receive human GH plus gonadotropin-releasing hormone (GnRH), the evidence includes an RCT and comparative case series. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. There are insufficient data on the incremental benefit of GH plus GnRH therapy in patients with precocious puberty. One RCT was published, but final height was not reported. One small comparative case series found significantly higher adult height with adjunctive GH therapy, but this study may have been subject to confounding. No studies reported functional or psychological outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are older adults with age-related growth hormone deficiency who receive human GH, the evidence includes a systematic review (TEC Assessment). Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. A TEC Assessment concluded there is a lack of evidence that GH therapy in older adults improves health outcomes. No subsequent controlled studies were identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cystic fibrosis who receive human GH, the evidence includes RCTs and a systematic review. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. Several RCTs and systematic reviews have been published. The RCTs were heterogenous and reported various outcomes. One systematic review did not pool outcomes on most outcomes, including frequency of intravenous antibiotic treatment, quality of life, and bone fracture; but the single pooled analysis found fewer hospitalizations in patients receiving GH therapy versus no treatment or placebo. The evidence is insufficient to determine the effects of the technology on health outcomes.

**PRACTICE GUIDELINES AND POSITION STATEMENTS**

**Pediatric Endocrine Society**

In 2015, the Pediatric Endocrine Society 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, patients 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 (GHRS) 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, 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 human growth hormone 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 (AACE) issued updated guidelines on growth hormone use in growth hormone-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.62 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.

In early 2016, results from the Growth Hormone Safety Workshop were published in the European Journal of Endocrinology.63 The workshop was convened by GHRS and other medical societies. The purpose of the workshop was to reappraise the safety of rhGH. The position statement concluded:

- After following children and adults for tens of thousands of person-years, the safety profile of rGH remains good when rhGH is used for approved indications and at recommended doses. There is no evidence supporting an association between rhGH and overall mortality, risk of new primary cancer, risk of recurrence of primary cancer, risk of stroke, or risk of cardiovascular disease.
- A carefully designed cohort study, providing continued long-term surveillance of patients treated with rhGH, would address the current limitations of safety data (eg, inconsistent definitions of outcomes, low incidence outcomes, and lack of dose-specific assessments).

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 deficiency64:

- “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.

ONGOING AND UNPUBLISHED CLINICAL TRIALS
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT01248416a</td>
<td>A Randomized Controlled Trial Of The Use Of Aromatase Inhibitors, Alone And In Combination With Growth Hormone In Adolescent Boys With Idiopathic Short Staturea</td>
<td>77</td>
<td>Oct 2017</td>
</tr>
<tr>
<td>NCT01246219a</td>
<td>The Influence Of Growth Hormone (GH) Therapy on Short Stature Related Distress a Prospective Randomized Controlled Triala</td>
<td>120</td>
<td>Dec 2017</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
a Denotes industry-sponsored or cosponsored trial.
CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>96372</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular</td>
</tr>
<tr>
<td>J2940</td>
<td>Injection, somatrem, 1 mg <em>(use this code for Protropin)</em></td>
</tr>
<tr>
<td>J2941</td>
<td>Injection, somatropin, 1 mg <em>(Use this code for Biotropin, Genotropin, Genotropin Miniquick, Humatrope, Norditropin, Nutropin, Nutropin AQ, Omnitrope, Saizen, Saizen [somatropin rDNA origin], Zorbtive)</em></td>
</tr>
<tr>
<td>Q0515</td>
<td>Injection, sermorelin acetate, 1 mcg</td>
</tr>
<tr>
<td>S9558</td>
<td>Home injectable therapy, growth hormone, including administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem</td>
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</table>

ICD-9 Diagnoses

<table>
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<th>Code</th>
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<tr>
<td>253.0</td>
<td>Acromegaly and gigantism</td>
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<tr>
<td>253.1</td>
<td>Other and unspecified anterior pituitary hyperfunction</td>
</tr>
<tr>
<td>253.2</td>
<td>Panhypopituitarism</td>
</tr>
<tr>
<td>253.3</td>
<td>Pituitary dwarfism</td>
</tr>
<tr>
<td>253.4</td>
<td>Other anterior pituitary disorders</td>
</tr>
<tr>
<td>253.6</td>
<td>Other disorders of neurohypophysis</td>
</tr>
<tr>
<td>253.7</td>
<td>Iatrogenic pituitary disorders</td>
</tr>
<tr>
<td>253.8</td>
<td>Other disorders of the pituitary and other syndromes of diencephalohypophysial origin</td>
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<tr>
<td>585.3</td>
<td>Chronic kidney disease (CKD), Stage III (Moderate)</td>
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<tr>
<td>585.4</td>
<td>Chronic kidney disease (CKD), Stage IV (Severe)</td>
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<tr>
<td>585.5</td>
<td>Chronic kidney disease (CKD), Stage V</td>
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<tr>
<td>585.6</td>
<td>End stage renal disease (ESRD)</td>
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<tr>
<td>585.9</td>
<td>Chronic kidney disease (CKD), unspecified</td>
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<tr>
<td>758.6</td>
<td>Gonadal dysgenesis (Turner's syndrome)</td>
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<tr>
<td>759.81</td>
<td>Prader-Willi syndrome</td>
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<tr>
<td>759.89</td>
<td>Other specified anomalies, other</td>
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ICD-10 Diagnoses *(Effective October 1, 2015)*

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<tr>
<td>B20</td>
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<tr>
<td>E22.0</td>
<td>Acromegaly and pituitary gigantism</td>
</tr>
<tr>
<td>E22.1</td>
<td>Hyperprolactinemia</td>
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<tr>
<td>E22.2</td>
<td>Syndrome of inappropriate secretion of antidiuretic hormone</td>
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<tr>
<td>E23.0</td>
<td>Hypopituitarism</td>
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<tr>
<td>E23.1</td>
<td>Drug-induced hypopituitarism</td>
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<tr>
<td>E23.6</td>
<td>Other disorders of pituitary gland</td>
</tr>
<tr>
<td>E24.1</td>
<td>Nelson's syndrome</td>
</tr>
<tr>
<td>E89.3</td>
<td>Postprocedural hypopituitarism</td>
</tr>
<tr>
<td>K91.2</td>
<td>Postsurgical malabsorption, not elsewhere classified</td>
</tr>
</tbody>
</table>
N18.3  Chronic kidney disease, stage 3 (moderate)
N18.4  Chronic kidney disease, stage 4 (severe)
N18.5  Chronic kidney disease, stage 5
N18.6  End stage renal disease
P70.4  Other neonatal hypoglycemia
R62.52 Short stature (child)
Q87.1  Congenital malformation syndromes predominately associated with short stature
Q96.9  Turner's syndrome, unspecified
T20.311A Burn of third degree of right ear [any part, except ear drum], initial encounter
T20.311D Burn of third degree of right ear [any part, except ear drum], subsequent encounter
T20.311S Burn of third degree of right ear [any part, except ear drum], sequela
T20.312A Burn of third degree of left ear [any part, except ear drum], initial encounter
T20.312D Burn of third degree of left ear [any part, except ear drum], subsequent encounter
T20.312S Burn of third degree of left ear [any part, except ear drum], sequela
T20.32XA Burn of third degree of lip(s), initial encounter
T20.32XD Burn of third degree of lip(s), subsequent encounter
T20.32XS Burn of third degree of lip(s), sequela
T20.33XA Burn of third degree of chin, initial encounter
T20.33XD Burn of third degree of chin, subsequent encounter
T20.33XS Burn of third degree of chin, sequela
T20.34XA Burn of third degree of nose (septum), initial encounter
T20.34XD Burn of third degree of nose (septum), subsequent encounter
T20.34XS Burn of third degree of nose (septum), sequela
T20.35XA Burn of third degree of scalp [any part], initial encounter
T20.35XD Burn of third degree of scalp [any part], subsequent encounter
T20.35XS Burn of third degree of scalp [any part], sequela
T20.36XA Burn of third degree of forehead and cheek, initial encounter
T20.36XD Burn of third degree of forehead and cheek, subsequent encounter
T20.36XS Burn of third degree of forehead and cheek, sequela
T20.37XA Burn of third degree of neck, initial encounter
T20.37XD Burn of third degree of neck, subsequent encounter
T20.37XS Burn of third degree of neck, sequela
T20.39XA Burn of third degree of multiple sites of head, face, and neck, initial encounter
T20.39XD Burn of third degree of multiple sites of head, face, and neck, subsequent encounter
T20.39XS Burn of third degree of multiple sites of head, face, and neck, sequela
T22.311A Burn of third degree of right forearm, initial encounter
T22.311D Burn of third degree of right forearm, subsequent encounter
T22.311S Burn of third degree of right forearm, sequela
T22.312A Burn of third degree of left forearm, initial encounter
T22.312D Burn of third degree of left forearm, subsequent encounter
T22.312S Burn of third degree of left forearm, sequela
T22.321A Burn of third degree of right elbow, initial encounter
T22.321D Burn of third degree of right elbow, subsequent encounter
T22.321S Burn of third degree of right elbow, sequela
T22.322A Burn of third degree of left elbow, initial encounter
T22.322D Burn of third degree of left elbow, subsequent encounter
T22.322S Burn of third degree of left elbow, sequela
T22.331A Burn of third degree of right upper arm, initial encounter
T22.331D Burn of third degree of right upper arm, subsequent encounter
T22.331S Burn of third degree of right upper arm, sequela
T22.332A Burn of third degree of left upper arm, initial encounter
T22.332D Burn of third degree of left upper arm, subsequent encounter
T22.332S Burn of third degree of left upper arm, sequela
T22.341A Burn of third degree of right axilla, initial encounter
T22.341D Burn of third degree of right axilla, subsequent encounter
T22.341S Burn of third degree of right axilla, sequela
T22.342A Burn of third degree of left axilla, initial encounter
T22.342D Burn of third degree of left axilla, subsequent encounter
T22.342S Burn of third degree of left axilla, sequela
T22.351A Burn of third degree of right shoulder, initial encounter
T22.351D Burn of third degree of right shoulder, subsequent encounter
T22.351S Burn of third degree of right shoulder, sequela
T22.352A Burn of third degree of left shoulder, initial encounter
T22.352D Burn of third degree of left shoulder, subsequent encounter
T22.352S Burn of third degree of left shoulder, sequela
T22.361A Burn of third degree of right scapular region, initial encounter
T22.361D Burn of third degree of right scapular region, subsequent encounter
T22.361S Burn of third degree of right scapular region, sequela
T22.362A Burn of third degree of left scapular region, initial encounter
T22.362D Burn of third degree of left scapular region, subsequent encounter
T22.362S Burn of third degree of left scapular region, sequela
T22.391A Burn of third degree of multiple sites of right shoulder and upper limb, except wrist and hand, initial encounter
T22.391D Burn of third degree of multiple sites of right shoulder and upper limb, except wrist and hand, subsequent encounter
T22.391S Burn of third degree of multiple sites of right shoulder and upper limb, except wrist and hand, sequela
T22.392A Burn of third degree of multiple sites of left shoulder and upper limb, except wrist and hand, initial encounter
T22.392D Burn of third degree of multiple sites of left shoulder and upper limb, except wrist and hand, subsequent encounter
T22.392S Burn of third degree of multiple sites of left shoulder and upper limb, except wrist and hand, sequela
T23.311A Burn of third degree of right thumb (nail), initial encounter
T23.311D Burn of third degree of right thumb (nail), subsequent encounter
T23.311S Burn of third degree of right thumb (nail), sequela
T23.312A Burn of third degree of left thumb (nail), initial encounter
T23.312D Burn of third degree of left thumb (nail), subsequent encounter
T23.312S Burn of third degree of left thumb (nail), sequela
T23.321A Burn of third degree of single right finger (nail) except thumb, initial encounter
T23.321D Burn of third degree of single right finger (nail) except thumb, subsequent encounter
T23.321S Burn of third degree of single right finger (nail) except thumb, sequela
T23.322A Burn of third degree of single left finger (nail) except thumb, initial encounter
T23.322D Burn of third degree of single left finger (nail) except thumb, subsequent encounter
T23.322S Burn of third degree of single left finger (nail) except thumb, sequela
T23.331A Burn of third degree of multiple right fingers (nail), not including thumb, initial encounter
T23.331D Burn of third degree of multiple right fingers (nail), not including thumb, subsequent encounter
T23.331S  Burn of third degree of multiple right fingers (nail), not including thumb, sequela
T23.332A  Burn of third degree of multiple left fingers (nail), not including thumb, initial encounter
T23.332D  Burn of third degree of multiple left fingers (nail), not including thumb, subsequent encounter
T23.332S  Burn of third degree of multiple left fingers (nail), not including thumb, sequela
T23.341A  Burn of third degree of multiple right fingers (nail), including thumb, initial encounter
T23.341D  Burn of third degree of multiple right fingers (nail), including thumb, subsequent encounter
T23.341S  Burn of third degree of multiple right fingers (nail), including thumb, sequela
T23.342A  Burn of third degree of multiple left fingers (nail), including thumb, initial encounter
T23.342D  Burn of third degree of multiple left fingers (nail), including thumb, subsequent encounter
T23.342S  Burn of third degree of multiple left fingers (nail), including thumb, sequela
T23.351A  Burn of third degree of right palm, initial encounter
T23.351D  Burn of third degree of right palm, subsequent encounter
T23.351S  Burn of third degree of right palm, sequela
T23.352A  Burn of third degree of left palm, initial encounter
T23.352D  Burn of third degree of left palm, subsequent encounter
T23.352S  Burn of third degree of left palm, sequela
T23.361A  Burn of third degree of back of right hand, initial encounter
T23.361D  Burn of third degree of back of right hand, subsequent encounter
T23.361S  Burn of third degree of back of right hand, sequela
T23.362A  Burn of third degree of back of left hand, initial encounter
T23.362D  Burn of third degree of back of left hand, subsequent encounter
T23.362S  Burn of third degree of back of left hand, sequela
T23.371A  Burn of third degree of right wrist, initial encounter
T23.371D  Burn of third degree of right wrist, subsequent encounter
T23.371S  Burn of third degree of right wrist, sequela
T23.372A  Burn of third degree of left wrist, initial encounter
T23.372D  Burn of third degree of left wrist, subsequent encounter
T23.372S  Burn of third degree of left wrist, sequela
T23.391A  Burn of third degree of multiple sites of right wrist and hand, initial encounter
T23.391D  Burn of third degree of multiple sites of right wrist and hand, subsequent encounter
T23.391S  Burn of third degree of multiple sites of right wrist and hand, sequela
T23.392A  Burn of third degree of multiple sites of left wrist and hand, initial encounter
T23.392D  Burn of third degree of multiple sites of left wrist and hand, subsequent encounter
T23.392S  Burn of third degree of multiple sites of left wrist and hand, sequela
T24.301A  Burn of third degree of unspecified site of right lower limb, except ankle and foot, initial encounter
T24.301D  Burn of third degree of unspecified site of right lower limb, except ankle and foot, subsequent encounter
T24.301S  Burn of third degree of unspecified site of right lower limb, except ankle and foot, sequela
T24.302A  Burn of third degree of unspecified site of left lower limb, except ankle and foot, initial encounter
T24.302D  Burn of third degree of unspecified site of left lower limb, except ankle and foot, subsequent encounter
T24.302S  Burn of third degree of unspecified site of left lower limb, except ankle and foot, sequela
T24.311A  Burn of third degree of right thigh, initial encounter
T24.311D  Burn of third degree of right thigh, subsequent encounter
T24.311S  Burn of third degree of right thigh, sequela
T24.312A  Burn of third degree of left thigh, initial encounter
T24.312D  Burn of third degree of left thigh, subsequent encounter
T24.312S  Burn of third degree of left thigh, sequela
T24.321A  Burn of third degree of right knee, initial encounter
T24.321D  Burn of third degree of right knee, subsequent encounter
T24.321S  Burn of third degree of right knee, sequela
T24.322A  Burn of third degree of left knee, initial encounter
T24.322D  Burn of third degree of left knee, subsequent encounter
T24.322S  Burn of third degree of left knee, sequela
T24.331A  Burn of third degree of right lower leg, initial encounter
T24.331D  Burn of third degree of right lower leg, subsequent encounter
T24.331S  Burn of third degree of right lower leg, sequela
T24.332A  Burn of third degree of left lower leg, initial encounter
T24.332D  Burn of third degree of left lower leg, subsequent encounter
T24.332S  Burn of third degree of left lower leg, sequela
T24.391A  Burn of third degree of multiple sites of right lower limb, except ankle and foot, initial encounter
T24.391D  Burn of third degree of multiple sites of right lower limb, except ankle and foot, subsequent encounter
T24.391S  Burn of third degree of multiple sites of right lower limb, except ankle and foot, sequela
T24.392A  Burn of third degree of multiple sites of left lower limb, except ankle and foot, initial encounter
T24.392D  Burn of third degree of multiple sites of left lower limb, except ankle and foot, subsequent encounter
T24.392S  Burn of third degree of multiple sites of left lower limb, except ankle and foot, sequela
T25.311A  Burn of third degree of right ankle, initial encounter
T25.311D  Burn of third degree of right ankle, subsequent encounter
T25.311S  Burn of third degree of right ankle, sequela
T25.312A  Burn of third degree of left ankle, initial encounter
T25.312D  Burn of third degree of left ankle, subsequent encounter
T25.312S  Burn of third degree of left ankle, sequela
T25.321A  Burn of third degree of right foot, initial encounter
T25.321D  Burn of third degree of right foot, subsequent encounter
T25.321S  Burn of third degree of right foot, sequela
T25.322A  Burn of third degree of left foot, initial encounter
T25.322D  Burn of third degree of left foot, subsequent encounter
T25.322S  Burn of third degree of left foot, sequela
T25.331A  Burn of third degree of right toe(s) (nail), initial encounter
T25.331D  Burn of third degree of right toe(s) (nail), subsequent encounter
T25.331S  Burn of third degree of right toe(s) (nail), sequela
T25.332A  Burn of third degree of left toe(s) (nail), initial encounter
T25.332D  Burn of third degree of left toe(s) (nail), subsequent encounter
T25.332S  Burn of third degree of left toe(s) (nail), sequela
T25.391A  Burn of third degree of multiple sites of right ankle and foot, initial encounter
T25.391D  Burn of third degree of multiple sites of right ankle and foot, subsequent encounter
T25.391S  Burn of third degree of multiple sites of right ankle and foot, sequela
T25.392A  Burn of third degree of multiple sites of left ankle and foot, initial encounter
T25.392D  Burn of third degree of multiple sites of left ankle and foot, subsequent encounter
T25.392S  Burn of third degree of multiple sites of left ankle and foot, sequela

REVISIONS

01-30-2014  Both Pediatric and Adult Growth Hormone medical policies have been incorporated into the newly titled "Human Growth Hormone" medical policy.

Updated Description section.

In Policy section:
- Pediatric Growth Hormone policy language was revised from the following:
  Growth hormone is contractually excluded except for the following specific situations:
  1. Deficiency
     Growth hormone has been approved for reimbursement subject to meeting all of the following criteria:
     a. Failure to respond (GH less than 10 ng/ml) to two hormones secretagogues (arginine, clonidine, glucagon, insulin, or levodopa)
     b. Growth failure as defined by the following age groups:
        0 - 6 months: <34 cm/year
        6 - 12 months: <15 cm/year
        1 - 3 years: <12 cm/year
        Over three years to puberty (see definition of puberty below): <5 cm/year
        Puberty (defined as bone age of 10 1/2 - 12 years for girls and bone age of 12 1/2 - 14 1/2 years for boys): <6 cm/year
     Note: Growth rates should be tracked over at least one year.
     Note: Continuation of treatment with growth hormone therapy requires a growth rate above 2.5 cm/year.
  2. Insufficiency or Partial Deficiencies
     Growth hormone has been approved for reimbursement subject to meeting all of the following criteria:
     a. Failure to respond (GH less than 15 ng/ml) to two hormones secretagogues (arginine, clonidine, glucagon, insulin, or levodopa)
     b. Height less than the 2.5 percentile
     c. Growth failure as defined by the following age groups:
        0 - 6 months: <34 cm/year
        6 - 12 months: <15 cm/year
        1 - 3 years: <12 cm/year
        Over three years to puberty (see definition of puberty below): <5 cm/year
        Puberty (defined as bone age of 10 1/2 - 12 years for girls and bone age of 12 1/2 - 14 1/2 years for boys): <6 cm/year
     Note: Growth rates should be tracked over at least one year.
     Note: Continuation of treatment with growth hormone therapy requires a growth rate above 2.5 cm/year.
  3. Panhypopituitarism
     Growth hormone has been approved for reimbursement subject to meeting all of the following criteria:
     a. Deficiencies of 2 or more other pituitary hormones (TSH, ACTH, FSH/LH, antidiuretic hormone)
     b. Low values for IGF-1
     Note: Growth hormone stimulation testing is not required in these cases.
Note: Growth hormone therapy may be approved for life.

4. Turner, Prader-Willi, and Noonan Syndromes With Growth Failure
   Growth hormone has been approved for reimbursement subject to meeting all of the following criteria:
   a. Height less than the 2.5 percentile for age and sex
   b. Growth failure as defined by the following age groups:
      • 0 - 6 months: < 34 cm/year
      • 6 - 12 months: < 15 cm/year
      • 1 - 3 years: <12 cm/year
      • Over three years to puberty (see below definition of puberty): <5 cm/year
      • Puberty (defined as bone age of 10 1/2-12 years for girls and bone age of 12 1/2 -14 1/2 years for boys): <6 cm/year
      Note: Growth rates should be tracked over at least one year.
   Note: Growth hormone stimulation testing is not required in these cases.

5. Managing Ongoing Renal Dialysis Patients With Growth Failure
   Growth hormone has been approved for reimbursement subject to meeting all of the following criteria:
   a. End stage renal disease with GFR less than 75 ml/min/1.73m2 prior to successful transplant
   b. Under age 18
   c. With open epiphyses
   d. Height less than the 2.5 percentile for age and sex
   e. Growth failure as defined by the following age groups:
      • 0 - 6 months: <34 cm/year
      • 6 - 12 months: < 15 cm/year
      • 1 - 3 years: <12 cm/year
      • Over three years to puberty (see below definition of puberty): <5 cm/year
      • Puberty (defined as bone age of 10 1/2-12 years for girls and bone age of 12 1/2 -14 1/2 years for boys): <6 cm/year
      f. Complicating factors have been treated including malnutrition and acidosis
      Note: Growth rates should be tracked over at least one year.
      Note: Growth Hormone stimulation testing is not required.

Termination of Growth Hormone Therapy
Growth hormone therapy is no longer covered when any one of the following criteria is met:
1. Epiphyseal fusion has occurred
2. Mid-parental height is achieved. Mid-parental height = (father’s height + mother’s height) divided by 2, plus 2.5 inches (6.4 cm) (male) or minus 2.5 inches (6.4 cm) (female)
3. Failure to respond to growth hormone therapy with a growth rate of less than 2.5 cm/year
NOTE: When a consultant recommends that growth hormone treatment be given for the life of the patient, it will no longer be necessary to re-review for medical necessity. It will be necessary, however, to review for benefits. Such instances may include:
   1. Panhypopituitarism, or
   2. When adult growth hormone therapy requirements are met (see Adult Growth Hormone policy)

Documentation needed for predetermination are:

   DOCUMENTATION
   • Growth charts with at least 3 measurements over at least one year
   • Growth hormone stimulation testing results

   Adult Growth Hormone policy language was revised from the following:
   1. Growth hormone therapy is excluded for insureds over the age of 18 with the following exceptions:
Human Growth Hormone

<table>
<thead>
<tr>
<th>a. Those Insureds over the age 18 with:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Demonstrated hypothalamic or pituitary disease or injury; and</td>
</tr>
<tr>
<td>• Laboratory proven growth hormone deficiency</td>
</tr>
<tr>
<td>b. Those Insureds over the age of 18 who have had childhood onset of growth hormone deficiency and have had that deficiency demonstrated by testing during childhood.</td>
</tr>
<tr>
<td>c. Those Insureds over the age 18 with Panhypopituitarism with deficiencies of 3 or more other pituitary hormones (TSH, ACTH, FSH/LH, antidiuretic hormone) and low values for IGF-1.</td>
</tr>
</tbody>
</table>

2. Growth hormone deficiency must be documented by the following criteria:
   a. Biochemical testing by means of a subnormal response to standard growth hormone stimulation test (peak growth hormone values <5ng/ml to provocative stimuli). Insulin tolerance test with documented hypoglycemia (blood sugars less than 40mg/dl or 50% decrease from baseline) with symptoms is the standard test. When Insulin Tolerance test is contraindicated in a given insured, Growth Hormone Releasing Hormone/arginine can be used as an alternate testing procedure. L-dopa, glucagon or clonidine is not acceptable secretagogues in adults.
   OR
   b. A below normal level of IGF-1 (less than 84 μg/liter) constitutes laboratory proof of growth hormone deficiency when associated with panhypopituitarism with documented multiple hormone deficiencies (3 or more deficiencies: secondary hypothyroidism, ACTH deficiency, gonadotropin deficiency, diabetes insipidus) as a result of pituitary or hypothalamic disease secondary to tumor, surgery, inflammation, radiation therapy, severe head trauma or structural abnormality (septo-optic dysplasia, ectopic neurohypophysis). Growth hormone stimulation testing is not necessary in these cases.

3. Continuation of approval for growth hormone therapy requires some indication of a clinical response to the growth hormone during the first 12 months of therapy; weight loss, improvement on lipid profile, increased bone mass, increased muscle strength or increase of IGF1 into the normal range. Children on growth hormone therapy who continue growth hormone therapy into adulthood or adults with hypopituitarism of recent onset will not exhibit the sequelae of adult growth hormone deficiency and will not show the improvements listed above.

NOTE: If consultant decides that growth hormone treatment will be given for the rest of the life of the patient, it will no longer be necessary for Medical Review to re-review for medical necessity. It will be necessary, however, to review for benefits.

**UTILIZATION**

If growth hormone is approved for an adult, and there has been demonstrative clinical improvement maintained for 1 year or more, periodic review beyond that will be unnecessary for these adults.

Updated Rationale section.

In Coding section:
- Removed CPT code 90772 (Deleted code 01-01-2009).
- Added ICD-10 diagnosis codes. *(Effective October 1, 2014)*

Updated References section.

| 12-09-2014 | Updated Description section. |
| 06-23-2015 | Updated Description section. |

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<table>
<thead>
<tr>
<th>Date</th>
<th>Updated Description section.</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-08-2015</td>
<td>Updated Rationale section.</td>
</tr>
<tr>
<td></td>
<td>Updated References section.</td>
</tr>
<tr>
<td>01-01-2017</td>
<td>Updated Description section. In Policy section:</td>
</tr>
</tbody>
</table>
|           |   - Added Item A 5, "Neonate (≤4 months of age) with hypoglycemia in the absence of metabolic disorder AND growth hormone level is <20 ng/mL."
|           |   - Added Item A 6, "AIDS wasting."                                                          |
|           |   - Added Item A 7, "Prevention of growth delay in children with severe burns (see Policy Guidelines)."
|           |   - Added Item A 8, "Short bowel syndrome receiving specialized nutritional support in conjunction with optimal management of short bowel syndrome (see Policy Guidelines)."
|           |   - Added Item B 4, "AIDS wasting."                                                          |
|           |   - Added Item B 5, "Promotion of wound healing in patients with severe burns (see Policy Guidelines)."
|           |   - Added Item B 6, "Short bowel syndrome receiving specialized nutritional support in conjunction with optimal management of short bowel syndrome (see Policy Guidelines)."
|           |   - In Policy Guidelines Item 3, added "Sleep studies are recommended prior to initiation of growth hormone therapy for obese pediatric patients with Prader-Willi syndrome."
|           |   - Added Policy Guidelines Items 5, 6, and 7.                                                 |
|           |   - Added Policy Guidelines Item 8 e, "Neonatal hypoglycemia related to growth hormone deficiency."
|           |   - In Policy Guidelines Item 8, added "Children, Adolescents and Adults: a. AIDS wasting syndrome b. Short Bowel syndrome c. Severe burn patients" |
|           | Updated Rationale section. In Coding section:                                                 |
| 05-24-2017| Updated Description section.                                                                  |
| 08-18-2017| In Policy section:                                                                           |
|           |   - In Item A 1, added "as defined by" and removed "meeting the following criteria" to read, "Growth Hormone or Insufficiency as defined by:"|
|           |   - In Item A 4, added "Chronic Renal Insufficiency or End Stage Renal Disease" and "as defined by" and removed "Managing Ongoing Renal Dialysis Patients With Growth Failure" and "subject to meeting all of the following criteria" to read, "Chronic Renal Insufficiency or End Stage Renal Disease as defined by:"|
|           |   - Added new Item A 4 a, "Chronic renal insufficiency defined as GFR less than 60 mL/min/1.73 m² prior to successful transplant"
|           |   - In new Item A 4 b (previous Item A 4 a), added "defined as" and removed "with" to read, "End stage renal disease defined as serum creatinine greater than 1.5 mg/dL or GFR less than 75 mL/min/1.73 m² prior to successful transplant"
|           |   - Removed previous Item A 4 b, "Under age 18"
|           |   - In Item A Termination of Growth Hormone Therapy, removed "no longer covered"
and added “not medically necessary” to read, “Growth hormone therapy is not medically necessary when any of the following criteria is met.”

REFERENCES

Contains Public Information


Other References

**Pediatric Growth Hormone**

1. Blue Cross and Blue Shield of Kansas Family Practice Liaison Committee, July 2006 (BlueShield Report. MAC-03-06); July 2007.
2. Blue Cross and Blue Shield of Kansas Pediatric Liaison Committee, August 2006 (see BlueShield Report. MAC-03-06); August 2007; July 2011; July 2013.
3. Blue Cross and Blue Shield of Kansas Medical Advisory Committee (MAC), November 2006 (BlueShield Report. MAC-03-06); November 2007.
9. Blue Cross and Blue Shield of Kansas, Pediatric Liaison Committee CB, October 2013.

**Adult Growth Hormone**

1. Blue Cross and Blue Shield of Kansas Internal Medicine Liaison Committee, August 2006 (See BCBSKS Newsletter, Blue Shield Report. MAC-03-06); August 2013.
2. Blue Cross and Blue Shield of Kansas Medical Advisory Committee (MAC), November 2006 (BCBSKS Newsletter, Blue Shield Report. MAC-03-06).
3. Blue Cross and Blue Shield of Kansas, Internal Medicine Liaison Committee CB, October 2013

**Human Growth Hormone**

1. Blue Cross and Blue Shield of Kansas Internal Medicine Liaison Committee, August 2014.
2. Blue Cross and Blue Shield of Kansas Pediatric Liaison Committee, July 2014.