Human Growth Hormone

Policy # 00188
Original Effective Date: 06/21/2006
Current Effective Date: 09/19/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider recombinant human growth hormone (rhGH) therapy to be **eligible for coverage.**

Patient Selection Criteria
The use of recombinant human growth hormone (rhGH) therapy may be considered **eligible for coverage** for any of the following indications:

- Children with proven growth hormone deficiency (GHD)
- Children with height less than the 3rd percentile for chronologic age with chronic renal insufficiency
- Patients with acquired immunodeficiency syndrome (AIDS) wasting
- Adults with proven growth hormone deficiency (GHD)
- Patients with Turner's syndrome
- Children with growth failure due to Prader-Willi syndrome
- Patients with short stature due to Noonan syndrome
- Promotion of wound healing in burn patients
- Prevention of growth delay in children with severe burns
- Patients with short bowel syndrome receiving specialized nutritional support in conjunction with optimal management of short bowel syndrome
- Children with short stature due to short stature homeobox-containing gene (SHOX) deficiency

In addition to meeting the indication criteria:

- Patients must be prescribed Humatrope, Nutropin, or Norditropin prior to other growth hormone (GH) products (unless there is clinical evidence or patient history that suggests the use of these products will be ineffective or cause an adverse reaction to the patient).
  (Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary ******** *if not met.)*

Note: See U. S. Food and Drug Administration (FDA) labeled drug indications (grid) for specific conditions listed in the patient selection criteria above.

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When Services Are Considered Not Medically Necessary
The following U. S. Food and Drug Administration (FDA)-approved indications or situations are considered **not medically necessary:**

- Pediatric patients born small for gestational age (SGA) who fail to show catch-up growth by age two.
- Children with height standard deviation score (SDS) of -2.25 or below without documented growth hormone deficiency (GHD).
- Use of growth hormone (GH) products other than Humatrope, Nutropin, or Norditropin.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of recombinant human growth hormone (rhGH) therapy to be **investigational*** for other indications, including, but not limited to:

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

Policy Guidelines

The numbered guidelines correspond to the indications listed in the coverage section above.
Medically Necessary Indications:

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

For adults, proven GHD is defined as:

a. An abnormal response to TWO provocative stimulation tests, such as L-dopa, clonidine, glucagons, arginine, GH-releasing hormone (GHRH), or insulin. The insulin tolerance test is considered the best predictor of GHD; however, this test is contraindicated in patients with seizures or coronary artery disease. A provocation test using arginine and GHRH is also acceptable and is considered more stringent than tests using arginine alone or levodopa alone. Although an abnormal GH response has been traditionally defined as less than 10ng/mL, different tests have different potencies, and the cutoff is likely to be lower when using monoclonal-based GH assays and rhGH reference preparations. Twenty-four hour continuous measurements of GH, serum levels of insulin-like growth factor (IGF-I), or serum of levels insulin-like growth factor-binding protein (IGFBP) are considered inadequate to document GHD.
b. An abnormal response to ONE provocative stimulation test in patients with defined central nervous system pathology, history of irradiation, multiple pituitary hormone deficiency, or a genetic defect.
c. Low IGF-I concentration in patients with complete hypopituitarism.

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

2. Chronic renal insufficiency is defined as a serum creatinine of greater than 1.5mg/dL (or 1.4 for women and 1.7 for men) or a creatinine clearance $\leq$ 75mL/min per $1.73m^2$. In patients with chronic renal failure undergoing transplantation, GH therapy is discontinued at the time of transplant or when the growth velocity is less than 2cm per year, when epiphyseal fusion has occurred, or when the height reaches the 5^{th} percentile of adult height.
3. Acquired immunodeficiency syndrome wasting is defined as a greater than 10% of baseline weight loss that cannot be explained by a concurrent illness other than HIV infection. Patients treated with GH must simultaneously be treated with antiviral agents. Therapy is continued until this definition is no longer met.
4. Adults with GHD are defined as in No. 1 above. Only about 25% of those children with documented GHD will be found to have GHD as adults. Therefore, once adult height has been achieved, subjects should be retested for GHD to determine if continuing replacement therapy is necessary. These transition patients who require further treatment are usually started at doses of 0.4 to 0.8mg/day, and titered to maintenance doses of 1.2 to 2.0mg/day. Adults with GHD not related to idiopathic deficiency of childhood (e.g., pituitary tumor, pituitary surgical damage, irradiation, trauma) are usually started at 0.1 to 0.3mg/day; the dose is titered to clinically desired end points (improved body composition, quality of life, reduction in cardiovascular risk factors), usually

resulting in maintenance doses of 0.2 to 0.5mg/day for men and 0.4 to 1.0mg/day for women. The FDA cautions that the safety and effectiveness of GH therapy in adults aged 65 and over has not been evaluated in clinical studies. Therefore, it is noted that elderly patients may be more sensitive to the action of GH therapy and may be more prone to develop adverse reactions.

5. Turner's syndrome is defined as a 45, XO genotype.
6. Prader-Willi syndrome is a genetic disorder characterized by a microdeletion in the long arm of chromosome 15. Clinically, the syndrome presents as a complex multisystem disorder characterized by excessive appetite, obesity, short stature, characteristic appearance, developmental disability, and significant behavioral dysfunction. Growth hormone deficiency has been demonstrated in most tested patients with Prader-Willi syndrome.

Sleep studies are recommended prior to initiation of GH therapy for obese pediatric patients with Prader-Willi syndrome.

7. GH therapy for burn patients should be limited to those patients with 3rd-degree burns.
8. Children with severe burns have been successfully treated with 0.05 to 0.2mg/kg rhGH per day during acute hospitalization and for up to 1 year after burn.
9. GH for patients with short bowel syndrome should be limited to patients receiving specialized nutritional support in conjunction with optimal management of short bowel syndrome. Specialized nutritional support may consist of a high-carbohydrate, low-fat diet adjusted for individual patient requirements. Optimal management may include dietary adjustments, enteral feedings, parenteral nutrition, fluid, and micronutrient supplements. Zorbtive is administered daily at 0.1mg/kg subcutaneously up to 8mg/day. Administration of Zorbtive for longer than 4 weeks has not been adequately studied per the FDA indications.

Not Medically Necessary Indications:

1. Pediatric patients born SGA. There are no established criteria for SGA or "catch-up" growth. However, in the data submitted to the FDA as part of the approval process, the mean height of enrolled patients was at least 2 SDs below the mean. Absence of catch-up growth was defined as a height velocity below 1 SDS, adjusted for age.
2. Pediatric patients with short stature. "Short stature" has been defined by the American Association of Clinical Endocrinologists and the Growth Hormone Research Society as height more than 2 SDs below the mean for age and sex. The FDA-approved indication is for children with a height SDS of -2.25 below the mean. Using this proposed definition, approximately 1.2% of all children would be defined as having idiopathic short stature and considered potentially treatable under these indications. Note that this indication is considered not medically necessary.

Background/Overview

HGH, also known as somatotropin, is synthesized in somatotropic cells of the anterior lobe of the pituitary gland. GHD can occur due to a variety of conditions, such as:

- Pituitary tumor

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

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

A major point of controversy is what defines "inadequate secretion of normal endogenous growth hormone," and what constitutes "growth failure." Prior to the availability of biosynthetic GH, GH was rationed to children with classic GHD, as defined by a subnormal response (< 10ng/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 (CDGD), or idiopathic short stature. "Classic" GHD is suggested when the abnormal growth velocity (typically below the 10th percentile) or height is more than 2 SDSs below the current population mean, in conjunction with a chronological age that is greater than the height age and bone age. In practical fact, 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.

However, 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 the parent due to their particular psychosocial concerns regarding height.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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

Beginning in 1985, recombinant GH has been marketed for a variety of U.S. FDA -labeled indications as follows:

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	Genotropin (Pharmacia)	Humatrope (Lilly)	Norditropin (Novo-ordisk)	Nutropin (Genentech)	Saizen (Serono)	Serostim (Serono)	Tev-Tropin/ Zomacrton (Ferring)	Zorbtive (Serono)	Omnitrope (Sandoz)
Growth failure, peds pts with inadequate endogenous GH	yes	yes	yes	yes	yes		yes		yes
Growth failure due to Prader-Willi syndrome	yes		yes						yes
Replacement therapy in adults with GHD	yes	yes	yes	yes	yes				yes
Growth failure associated with chronic renal insufficiency				yes					
HIV wasting or cachexia						yes			
Children born SGA, who fail to show catch-up growth by age 2 years	yes	yes	yes						yes
Short stature (height SDS $\leq$ -2.25) in non-GH-deficient peds pts	yes	yes		yes					
Short stature due to Turner's syndrome (45, XO)	yes	yes	yes	yes					yes
Treatment of short bowel syndrome								yes	
Short stature in peds pts with SHOX deficiency		yes							
Short stature in peds pts with Noonan syndrome			yes						

In 2001, Genotropin received an FDA-labeled indication for treatment of pediatric patients born SGA who fail to show catch-up growth by age 2 years. Most children born SGA 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. Growth hormone 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, the FDA approved a recombinant HGH 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 was the first indication that is based on short stature alone, without an underlying etiology.

Rationale/Source

Outcome Measures in Growth Hormone 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 not sufficient evidence to establish that short stature is associated with substantial impairments in psychological functioning or quality of life, nor is there evidence that increases in height improve these parameters. Similarly, improvements in other measures of body composition such as muscle mass or muscle strength are not in themselves sufficient to establish that health outcomes are improved. Therefore, for most conditions in this literature review, changes in other outcome measures such as functional status, quality of life, or disease-specific clinical outcomes, are necessary to demonstrate an improvement in health outcomes.

Safety of Growth Hormone Treatment

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

There is concern that GH treatment may increase the rate of malignancy, particularly de novo leukemia in patients without risk factors. To date, there is insufficient evidence of a causative relationship between GH treatment and malignancy rates. The largest study published to date on the association of GH treatment with malignancy includes data on 54,996 included in a post marketing surveillance registry established by Genentech, Inc. The most common indications for GH use among children in the database were idiopathic GHD (42.5%), idiopathic short stature (17.8%), organic GHD (15.2%), and Turner's syndrome (9.3%). As of January 1, 2006, a total of 4,084 adverse events (6.2%), including 1,559 (2.4%) serious adverse events and 174 (0.3%) deaths, had been reported. Investigators assessed 19 of 174 deaths (11% of deaths) as related to GH treatment. Twelve of the 19 GH-associated deaths were due to neoplasms (0.1% of children in the registry), and the other 7 deaths were each due to a different cause. Overall, intracranial malignancies of nonpituitary origin were reported in 243 patients; 44 were new-onset malignancies. In addition, extracranial malignancies, including leukemia, were reported in 87 patients; 63 were new-onset extracranial malignancies. The authors reported that 36 new-onset malignancies (intracranial and extracranial combined) occurred in individuals without risk factors; 29 of the 36 cases were confirmed as being enrolled in the

registry. The rate of new-onset malignancy did not exceed the rate expected in the general population (standard incidence ratio = 1.12, 95% confidence interval [CI]: 0.75 to 1.61). This study lacked a concurrent comparison with untreated patients to compare actual rates of malignancy and other adverse events.

In addition, a 2014 study did not find an increased risk of de novo malignancies in GH-treated patients who survived childhood cancer for at least 5 years. The study included 12,098 patients in the United States and Canada; 338 (2.8%) were verified users of GH treatment. Sixteen of 338 (4.7%) of GH-treated survivors and 203 (1.7%) non-GHC-treated survivors developed cancers of the central nervous system; the difference between groups was not statistically significant.

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

Growth Hormone Deficiency

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

Growth Hormone Deficiency in Children
In children with GHD, treatment increases growth velocity and final height. Root and colleagues followed approximately 20,000 children for a period of 9 years as part of the National Cooperative Growth Study (NCGS). Growth velocity improved compared to pre-treatment values, and this improvement was maintained for at least 4 years. For children who were treated for at least 7 years, there were improvements in the mean height SDSs that ranged from 1.3 to 2.5, depending on the specific underlying condition. If treatment is started at an early age, the majority of children can achieve a final height close to that expected from parental height. In a study of 1,258 patients in the Pfizer International Growth Database, the 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.

Growth Hormone Deficiency in Adults
In adults with GHD, there is evidence from RCTs that treatment leads to increases in lean body mass and decreases in body fat. Meta-analyses of RCTs have shown evidence for increases in muscle strength and exercise capacity, although this was not a robust finding across all studies. There is also evidence from a meta-analysis of 20 RCTs that GH therapy is associated with increased bone mineral density in adults with GHD. The evidence on other outcomes such as quality of life, lipid profiles, cardiovascular disease, and total mortality is not consistent and is insufficient to determine whether these outcomes are improved with treatment.

Growth Failure Due to Prader-Willi Syndrome
Most children with Prader-Willi syndrome have hypothalamic dysfunction and are GH deficient. Use of HGH for children with growth failure due to Prader-Willi syndrome is an FDA-approved indication. The value of testing for GHD before treatment in these patients is questionable. None of the clinical studies selected patients for treatment based on presence or absence of GH, 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 studies have shown patient improvements with use of GH. For example, a 2008 RCT reported by Festen and colleagues involving 42 infants and 49 prepubertal children (age 3 to 14 years), found that GH treatment significantly improved height, body mass index (BMI), head circumference, and body composition. In 2012, the investigators published cognitive outcomes in children participating in this trial. During the 2-year randomized study, the mean total IQ score and subtests did not change significantly from baseline in GH-treated children. In untreated children, there was no significant change in total IQ score but scores on 2 of 3 subtests significantly declined from baseline.

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

significant interaction effects on a model predicting motor development age using the Alberta Infant Motor Scale.

According to the drug prescribing information, GH therapy use has been associated with sudden death in children with Prader-Willi syndrome. These deaths occurred among children who were severely obese or had severe respiratory impairment; these are now considered to be contraindications to GH treatment use (see Background/Overview section of this policy).

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

Section Summary:
For patients with documented GH deficiency and clinical manifestations such as short stature, GH replacement has been shown to improve growth velocity and final height achieved. In addition, it can ameliorate the secondary manifestations of GH deficiency seen primarily in older children and adults. Therefore, GH replacement may be considered medically necessary for these indications. For children with Prader-Willi Syndrome and growth failure, GH deficiency is assumed, and GH replacement may be considered medically necessary without documentation of GH deficiency.

Conditions without Growth Hormone Deficiency

Growth Hormone Use in Children with Short Stature Associated with Chronic Renal Insufficiency

In 2013, Wu and colleagues published a meta-analysis of RCTs evaluating the impact of GH therapy on height outcomes following renal transplant in children age 0 to 18 years. Five trials with a total of 401 participants met the review's inclusion criteria (RCTs including renal allograft recipients between 0 and 18 years-old). Trials were published between 1996 and 2002. A meta-analysis found significantly improved height velocity at the end of a year in children taking GH compared to 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 one year, the pooled MD in height SDS was 0.68 (95% CI: 0.25 to 1.11, $p = 0.002$) in

favor of the GH group. There were no statistically significant differences between groups in the rate of rejection episodes or in renal function.

Previously, in 2012, Hodson and colleagues 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 pre-dialysis, on dialysis, or post-transplant. In addition, trials needed to compare GH treatment with placebo, no treatment or a different GH regimen and needed to include height outcomes. A total of 7 RCTs with 809 children met the review criteria. Study entry criteria varied e.g., ranging from less than 3rd percentile for chronological age to less than 50th percentile for chronological age. Overall, treatment with GH (28 IU/m2/week) 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 to control (MD: 3.88cm/year, 95% CI: 3.32 to 4.44).

An example of an individual RCT is the trial by Hokken-Koelega and colleagues conducted in the Netherlands. This was a double-blind placebo-controlled crossover trial in 20 prepubertal children with severe growth retardation and chronic renal failure. Entry criteria included height velocity less than the 25% percentile for chronological age. Patients received 6 months of subcutaneous injection of GH (4 IU/m2 per day) before or after 6 months of placebo injection. There was a 2.9cm greater increase in height velocity per 6 months with GH compared to 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 to baseline scores (-< 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 that was within the normal range for girls and boys, and GH therapy did not result in significant effects on parathyroid hormone concentration, and there were no radiological signs of renal osteodystrophy.

Growth Hormone Therapy as a Treatment of Altered Body Habitus Related to Antiretroviral Therapy for Human Immunodeficiency Syndrome Infection

There has been research interest in the use of GH to treat the 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 minimal published literature regarding the use of GH for this indication. The literature is dominated by letters to the editors and small case series. The largest case series was reported by Wanke and colleagues 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.

Growth Hormone Therapy for Turner's Syndrome

Short stature is almost universal in Turner's syndrome. Poor growth is evident in utero and further deceleration occurs during childhood and at adolescence. The mean adult height for those with Turner's syndrome is 58 inches (4 feet, 10 inches). Unlike Prader-Willi syndrome, GHD is not seen. The FDA

approvals for GH were based on the results of randomized, controlled clinical trials that included final adult height as the outcome. For example, a group of patients with Turner's syndrome given Humatrope at a dosage of 0.3mg/kg/week for a median of 4.7 years achieved a final height of 146.0 +/- 6.2cm (57.5 +/-2.25 inches) compared to an untreated control group who achieved a final height of 142.1 +/- 4.8cm (56 +/- 2 inches).

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

Growth Hormone Therapy for Short Stature Due to Noonan Syndrome
In 2015, Giacomozzi et al published a systematic review of literature on the effect of GH therapy on adult height. Included in the review were studies treating individuals with a diagnosis of Noonan syndrome with no other causes of short stature and a normal karyotype in females. In addition, studies needed to follow patients for at least 3 years. A total of 23 studies met the inclusion criteria; none were RCTs and only 1 was controlled. Three of the studies were case reports and the remainder were prospective or retrospective cohort studies. In the 1 controlled study (MacFarlane et al, 2001), over the 3 year followup, the GH treated group gained a mean of 3.3 cm more than the untreated group. Among the uncontrolled studies, 2 reported adult height. Mean height SDS was -2.8 (SD=0.6) and mean adult height SDS was -1.4 (SD=0.9). Two uncontrolled studies reported near-adult height which was -2.1 (SD=0.9). In addition, 2 studies reported a change in height SDS corresponding to 8.6 cm (SD=5.9). The data are limited by the paucity of controlled studies and lack of RCTs.

Growth Hormone Therapy for Children with Short Stature Due to Short Stature Homeobox-Containing Gene Deficiency
Treatment of children with short stature due to SHOX deficiency is an FDA-approved indication for GH therapy (Humatrope). A 2010 Health Technology Assessment on GH treatment of growth disorders in children conducted a systematic review and identified one RCT evaluating GH therapy for children with short stature due to SHOX. This industry-sponsored open-label multicenter study was published by Blum and colleagues in 2007. It included 52 pre-pubertal 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 (cm/year) was 8.7cm (SD: 0.3) in the GH therapy group and 5.2 (SD: 0.2) in the untreated group; the difference between groups was statistically significant ($p < 0.001$). Height gain over the 2-year treatment period was 16.4 (SD: 0.4)cm in the treatment group and 10.5 (0.4)cm in the untreated group; $p < 0.001$. No serious adverse events were reported for either of the two above groups of patients.

Growth Hormone Therapy for Severe Burns

A Cochrane systematic review, published in 2012, included RCTs evaluating the impact GH therapy on the healing rate of burn wounds. Thirteen trials were identified that compared GH therapy to another intervention or to placebo. Six of these included only children and 7 involved only adults. Twelve of the studies were placebo-controlled. Findings of 2 studies reporting wound healing time in days were pooled. The mean healing time was significantly lower in the GH-treated group compared to placebo (MD: -9.07 days, 95% CI: -4.39 to -13.76). The authors also conducted meta-analyses of studies that did not conduct survival analyses but did follow patients until their wounds healed. These analyses found significantly shorter healing time in patients who received GH therapy among adults (2 studies) and among children (2 studies). A pooled analysis of 5 studies did not find a statistically significant difference in mortality among patients receiving GH therapy and placebo (risk ratio [RR]: 0.53, 95% CI: 0.22 to 1.29). The mortality analysis was likely underpowered; the total number of deaths was 17. A pooled analysis of 3 studies involving adults found significantly shorter hospital stays in patients who received GH therapy compared to placebo (MD: -12:55 days, 95% CI: -17.09 to -8.00). In another pooled analysis, there was a significantly higher incidence of hyperglycemia in GH-treated patients compared to controls (RR: 2.65, 95% CI: 1.68-4.16).

One study that measured mortality was published by Knox and colleagues. This was an RCT in 54 adult burn patients who survived the first 7 post-burn days. Those patients showing difficulty with wound healing were treated with rhGH and compared to those healing at the expected rate with standard therapy. Mortality of rhGH-treated patients was 11% compared to 37% not receiving rhGH ($p = 0.027$). Infection rates were similar in both groups. Moreover, Singh and colleagues studied 2 groups of patients ($n = 22$) with comparable third-degree burns; those who received GH had improved wound healing and lower mortality (8% vs. 44%). Another placebo-controlled trial found no benefit to GH with regard to length of hospitalization in 24 adult patients with severe burns.

Growth Hormone Therapy to Prevent Growth Delay in Children with Severe Burns

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

Growth Hormone Therapy for the Treatment of HIV Wasting

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

Growth Hormone Therapy in Conjunction with Optimal Management of Short Bowel Syndrome
Short bowel syndrome is experienced by patients who have had half or more of the small intestine removed with resulting malnourishment because the remaining small intestine is unable to absorb enough water, vitamins, and other nutrients from food. The FDA label for Zorbtive indicates that GH has been shown in human clinical trials to enhance the transmucosal transport of water, electrolytes, and nutrients. The FDA approval for Zorbtive was based on the results of a randomized, controlled, Phase III clinical trial in which patients dependent on intravenous parenteral nutrition who received Zorbtive (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 the 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 (total n = 30) found a statistically significant difference in weight change when patients were treated with GH or placebo (MD, 1.66kg, 95% CI: 0.69 to 2.63, p = 0.0008).
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 one component of this therapy.

Growth Hormone Use in Small for Gestational Age Children
A meta-analysis of RCTs evaluating GH treatment for children born SGA was published in 2009. Four trials with a total of 391 children met the eligibility criteria (birth height or weight below 2 SDS and initial height less than 2 SDS). The GH dose ranged from 33 to 67ug/kg in the RCTs, and the 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. The adult height in the treated group was significantly higher than that of controls; MD = 0.9 SDS (5.7cm), p < 0001. There was no difference in adult height between the 2 doses of 33 and 67ug/kg per day. The authors commented that it is unclear whether the gain in adult height associated with GH treatment "is of sufficient clinical importance and value to warrant wide-spread treatment of short children born SGA…"

There are very minimal data regarding 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 above, data are inadequate to document that short-stature youths have either low self-esteem or a higher than average number of behavioral or emotional problems.

For both SGA children and short-stature children, an additional strategy to achieve target adult heights is to combine GH therapy with GnRH analogs, which prolong the prepubertal growth period. The combined therapy is intended to increase the critical pubertal height gain by delaying the fusion of the epiphyseal growth plates, thus prolonging the period during which GH is active. This therapy has been suggested for children who are considered short when they enter puberty.

Growth Hormone for Altered Body Habitus Related to Anti-retroviral Therapy for HIV Infection
There has been research interest in the use of GH to treat the 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 minimal published literature regarding the use of GH for this indication. The literature is dominated by letters to the editors and small case series. The largest case series was reported by Wanke et al who treated 10 HIV-infected patients with fat redistribution syndrome with GH for 3 months. The authors reported improved waist/hip ratio and mid-thigh circumference.

Growth Hormone Use in Children with Idiopathic Short Stature (i.e., without documented growth hormone deficiency or underlying pathology)

Impact of GH Treatment on Adult Height of Children With Idiopathic Short Stature
Several meta-analyses have been published. Most recently, Deodati and Cianfarani identified 3 RCTs and 7 non-RCTs. To be included in the meta-analysis, studies needed to include pre-pubertal children with initial short stature (more than 2 SDs below the mean) and peak GH response greater than 10ug/L. In addition, participants needed to have no previous GH therapy and no comorbid conditions that could impair growth. Adult height was defined as a growth rate of less than 1.5cm/year 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 a SDS, also known as a z-score. The investigators considered a MD in height of more than 0.9 SD scores (about 6cm) to be a satisfactory response to GH therapy. Only one of the RCTs was placebo-controlled, and that study had a high dropout rate (40% in the treated group and 65% in the placebo group).

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

In 2009, a Cochrane review of RCTs evaluating GH therapy for idiopathic short stature in children and adolescents was published. A total of 10 RCTs met eligibility criteria, which included being conducted in children who had normal GH secretion, normal size for gestational age at birth, and no evidence of chronic organic disease. In addition, studies needed to compare GH treatment to 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 to no treatment. Unlike the Deodati review described above, studies were not required to report final adult height. Nine out of 10 studies in the Cochrane review were short-term and reported intermediate outcomes. A pooled analysis of 3 studies reporting growth velocity at 1 year found a

statistically significantly greater growth velocity in treated compared to untreated children. The weighted mean difference (WMD) was 2.84 (95% CI: 2.06 to 2.90). Five studies reported height SDSs, but there was heterogeneity among studies and their findings were not pooled. These data suggest that GH has an effect on height in children with idiopathic short stature in the short term but that evidence on GH's effects on adult height is extremely limited.

Section Summary:
Recent systematic reviews have found that GH treatment may result in increases in 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 is in the range of 3-4cm, and children treated with GH remain below average in height, with heights that are between 1 and 2 SDs below the mean at the end of treatment. These studies do not follow treated patients long enough to determine the ultimate impact of GH on final adult height.

Impact of GH Treatment on Self-Esteem and Quality of Life in Children With Idiopathic Short Stature
Advocates of GH therapy often cite the potential psychosocial impairments associated with short stature. However, several RCTs have addressed this topic, and they have not found better self-esteem, psychological functioning, or quality of life in children treated with GH compared to controls. These studies are described briefly below:

In 2004, Ross and colleagues published findings on psychological adaptation in 68 children with idiopathic short stature without GHD. 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 1.5cm per year. At baseline and then yearly, parents and children completed several psychological instruments including the Child Behavior Checklist (CBCL) and Self-Perception Profile (SPP). No significant associations were found between attained height SDS or change in height SDS and annual changes in scores on the CBCL. There were no significant differences between groups on any CBCL summary scales in years 1 and 2, but in year 4, there were significantly higher scores on the CBCL summary scales in the group receiving GH treatment. There were no significant differences between groups on the SPP at any follow-up point. In conclusion, short stature in this study was not associated with problems in psychological adaptation or self-concept.

Theunissen and colleagues 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). 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 and colleagues examined the behavior of children without documented GHD who were treated with GH due to idiopathic short stature. Across measures of behavior, including IQ, self-esteem, self-

perception, or parental perceptions of competence, there were no significant differences between the control and 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.

In summary RCTs have not found that short stature is associated with psychological problems, in contrast to the expectations of some advocates. In addition, the available trials have not reported a correlation between increases in height and improvements in psychological functioning.

In light of the published research on the impact of GH on health outcomes for children with idiopathic short stature, and because this group of children is healthy (i.e., no identified pathology or hormone deficits) and thus should avoid unnecessary exposure to long-term medical treatment, GH treatment for children with idiopathic short stature is considered not medically necessary.

Growth hormone use in children with "genetic potential" (i.e., lower than expected height percentiles based on parents' height)

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

Growth Hormone Therapy in Conjunction with Gonadotropin-Releasing Hormone Therapy as a Treatment of Precocious Puberty
Precocious puberty is generally defined as the onset of secondary sexual characteristics before 8 years of age in girls and 9 years in boys. Central precocious puberty is related to hypothalamic pituitary gonadal activation, leading to increase in sex steroid secretion, which accelerates growth and causes premature fusion of epiphyseal growth plates, thus impacting final height. Children with precocious puberty are often treated with GnRH analogs to suppress the pituitary gonadal activity, to slow the advancement of bone age, and to improve adult height. Several long-term studies have reported that treatment with GnRH analogs is associated with improved adult height in most cases, particularly in those with the most accelerated bone age progression at treatment onset, the shortest predicted height, and the greatest difference between the target height and the predicted height. In contrast, patients with a slowly progressive form in which the predicted height does not change after 2 years of follow-up may not require any treatment. In another subset of patients, GnRH analog therapy may be associated with a marked deceleration of bone growth that may ultimately result in an adult stature that is less than the targeted midparental height. Growth hormone may be offered to these patients in order to achieve the targeted adult height. There have been no RCTs comparing final adult height in those treated with GnRH analogs alone versus GnRH analogs combined with GH therapy, and the largest case series includes 35 patients. Case series suggest that GH is most commonly offered as an adjunct to GnRH analogs when the growth velocity drops below the 25th percentile for chronologic age. A series of comparative case series that have included final adult heights have been reported by the same group of investigators from Italy. This group of investigators is the only one to have reported final adult heights. The most recent reports focus on a group of 17 girls with precocious puberty and a growth velocity below the 25th percentile who were treated with a combination of GnRH and GH, and

18 girls who refused treatment with adjunctive GH. Those in the combined group attained a significantly greater adult height (161.2 +/- 4.8cm) than the "control" group (156.7 +/- 5.7cm) This small study is inadequate to permit scientific conclusions. Tuvemo and colleagues reported on the results of a trial that randomized 46 girls with precocious puberty to receive either GnRH analogs or GnRH analogs in addition to GH. Of interest, all the participants were adopted from developing countries; precocious puberty is thought to be common in such cross-cultural adoptions. Criteria for participation in this trial did not include predicted adult height or growth velocity. After 2 years of treatment, the mean growth and predicted adult height were greater in those receiving combined treatment compared to those receiving GnRH analogs alone. The absence of final height data limits interpretation of this trial.

As noted here, the "not medically necessary" status of other applications of GH for non-GH deficient short-stature children is based on the absence of a functional impairment associated with a less than predicted final adult height. While these same considerations may apply to using GH therapy as a component of therapy for precocious puberty, the "investigational" status of this indication is based on lack of final height data from controlled trials.

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

Growth Hormone Therapy for Cystic Fibrosis
A 2013 Cochrane systematic review evaluated GH therapy for improving lung function, nutritional status and quality of life in children and young adults with cystic fibrosis. The authors identified 4 RCTs with a total of 161 participants. All of the studies used daily subcutaneous injection of recombinant GH as the intervention and included a no treatment or placebo control group. The studies all 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 to no treatment and the remaining trial compared GH alone to glutamine or glutamine plus GH. In one study, patients were treated with GH for 4 weeks and in the other studies, duration of treatment ranged from 6 months to 1 year. There were insufficient data to determine the effect of GH on most health outcomes including frequency of intravenous antibiotic treatment, quality of life, and bone fracture. Data were pooled on 1 outcome, frequency of hospitalizations. In trials with durations of at least 1 year, there was a significantly lower rate of

hospitalizations per year in the group receiving GH therapy (pooled effect size: -1.62, 95% CI: -1.98 to -1.26).

One of the RCTs was an industry-sponsored open-label study published by Stalvey and colleagues in 2012. This study compared GH therapy to no treatment in prepubertal children with cystic fibrosis who were younger than 14 years-old. The eligibility criteria included height no more than 10th percentile for age and sex; children with documented GHD were excluded. Participants were treated daily for 12 months and were followed for an additional 6 months. The study included 68 children; 62 (91%) were included in the efficacy analysis, and all but one were included in the safety analysis. Annualized height velocity at month 12 was 8.2cm/yr (SD: 2.1) in the treatment group and 5.3cm/yr (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 compared to the control group, $p < 0.001$. Between months 12 and 18 (after treatment ended), the control group remained at the same height SDS, and the treatment group experienced a slight decline (0.1 SDS), but maintained a 0.5 SDS advantage over the control group.

In terms of pulmonary outcomes, the unadjusted rate of change from baseline to 12 months in most variables (7 of 8 pulmonary test results) did not differ between groups. However, the unadjusted change from 12 months to 18 months (after treatment ended) was significantly greater in the control group than the treatment group in 4 of 7 pulmonary test variables including forced air volume in one second (FEV1) ($p < 0.005$) and forced vital capacity (FVC) ($p < 0.01$). In the treatment group, mean FEV1 was 1,209 (SD: 451) at baseline, 1,434 (SD: 539) at 12 months, and 1,467 (SD: 568) at 18 months. This compared with 1,400 (SD: 495) at baseline, 1,542 (SD: 510) at 12 months, and 1,674 (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. In general, treatment with GH resulted in statistically significant improvement in height SDS but did not significantly improve outcomes associated with cystic fibrosis. A limitation of this study was that it was not blinded; however, this is less of a potential bias in a study like this one that has objective outcomes such as height and hospitalization rate.

Section Summary:
GH treatment has been used in numerous conditions where there is not documented GHD. For some of these conditions that are associated with growth failure, such as Turner's syndrome, Noonan's syndrome, SHOX mutations, short-bowel syndrome, and children with renal insufficiency, there is FDA-approval for GH treatment, there is some clinical trial evidence that treatment leads to improved growth velocity and/or final height, and there is support for use of GH in clinical practice guidelines. The evidence is mixed on use of GH therapy for treating severe burns, with numerous trials and systematic reviews reporting improved healing times. Some, but not all, controlled studies have found improved clinical outcomes e.g. lower

mortality, and/or shorter hospital stay when GH therapy was used. Therefore, GH treatment may be considered medically necessary for these indications.

There are some FDA-approved indications for GH treatment in which there are no associated pathologic disorders. These include pediatric patients born SGA and children with height that is more than 2.25 SDs below the age-adjusted mean. For these situations, the use of GH replacement has not been demonstrated to have health outcome benefits other than improved height. Because of this lack of demonstrated health outcome benefits together with the potential for adverse effects, the use of GH treatment for these patients is considered not medically necessary.

For numerous other indications that are not FDA-approved, there is a variable amount of evidence reporting on the impact of GH replacement on height, but there is a lack of evidence establishing that outcomes other than height are improved. For these conditions, the use of GH treatment is considered investigational.

Ongoing Clinical Trials

Aromatase Inhibitors, Alone And In Combination With Growth Hormone In Adolescent Boys With Idiopathic Short Stature (ThrasherAI) (NCT01248416): This open-label trial is randomly assigning adolescent boys with idiopathic short stature (equal or less than -2SD for height) to one of 3 treatment groups: 1) aromatase inhibitors alone; 2) somatropin alone; or 3) combination of aromatase inhibitor and somatropin. Change in height will be assessed at 1 and 2 years. The estimated enrollment is 75 participants, and the estimated date of study completion is October 2017.

Short Stature-Related Distress (NCT01246219): This double-blind placebo-controlled trial is comparing psychological measures in participants with idiopathic short stature who are treated with GH therapy compared to placebo, compared to no treatment and compared to controls of normal height. Idiopathic short stature is defined as more than 2 SDs below the average height; boys between the ages of 8 and 13 years will be included. Individuals with mental retardation or psychiatric illness will be excluded. The estimated enrollment will be 120 participants, and the estimated date of study completion is December 2015.

Severe Decrease of Growth Velocity in Children With Anorexia Nervosa. Therapeutic Trial of Growth Hormone (OREX) (NCT01626833): This is a double-blind placebo-controlled trial that is evaluating GH for treating children with clinical anorexia nervosa diagnosed at least 1 year before the study. Growth velocity needs to be documented for at least 18 months before study inclusion. The primary outcome is growth velocity after 1 year of treatment. Expected enrollment is 20 individuals and the expected date of study completion is September 2016.

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Policy History

Original Effective Date: 06/21/2006
Current Effective Date: 09/19/2018
06/07/2006 Medical Director review

Human Growth Hormone

Policy # 00188
Original Effective Date: 06/21/2006
Current Effective Date: 09/19/2018

06/21/2006	Medical Policy Committee approval
08/09/2006	Medical Policy Committee approval. Criteria clarifications were made; adult and child growth hormone deficiency sections were combined and abnormal GH response levels definitions confirmed as: “less than 10ng/ml for children and less than 5ng/ml for adults”.
09/03/2008	Medical Director review
09/17/2008	Medical Policy Committee approval. Noonan syndrome changed from investigational to eligible for coverage. Removed growth failure requirement from Prader-Willi syndrome criteria, and removed short stature requirement from Noonan syndrome criteria. FDA drug grid updated.
09/03/2009	Medical Policy Committee approval.
09/16/2009	Medical Policy Implementation Committee approval. No change to coverage eligibility.
09/09/2010	Medical Policy Committee review
09/15/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/01/2011	Medical Policy Committee review
09/14/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/06/2012	Medical Policy Committee review
09/19/2012	Medical Policy Implementation Committee approval. Added “growth failure due to” to the coverage criteria for Prader-Willi syndrome; Added “short stature due to” to the coverage criteria for Noonan syndrome; added “without documented growth hormone deficiency” to the Not Medically Necessary indication for children with height standard deviation score of -2.25 or below; added “recombinant” to describe human growth hormone therapy to the investigational statement; added juvenile chronic arthritis and treatment of children with “genetic potential” (i.e., lower than expected height percentiles based on parents’ height).
10/10/2013	Medical Policy Committee review
10/16/2013	Medical Policy Implementation Committee approval. In eligible for coverage statement, ’patients’ with growth failure due to Prader-Willi syndrome changed to ‘children’ with growth failure due to Prader-Willi syndrome. Children with short stature due to SHOX (short stature homeobox-containing gene) deficiency added to patient selection criteria (this is a FDA-approved indication). Added criteria that Humatrope, Nutropin, and Norditropin be prescribed before other growth hormone products.
11/06/2014	Medical Policy Committee review
11/21/2014	Medical Policy Implementation Committee approval. No change to coverage.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015	Medical Policy Committee review
11/16/2015	Medical Policy Implementation Committee approval. Tev-Tropin is transitioning to the name Zomacton. Updated in the product chart. Updated background info sections.
11/03/2016	Medical Policy Committee review
11/16/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
09/07/2017	Medical Policy Committee review
09/20/2017	Medical Policy Implementation Committee approval. No change to coverage.
09/06/2018	Medical Policy Committee review
09/19/2018	Medical Policy Implementation Committee approval. Updated FDA approved indication chart. No coverage changes.

Next Scheduled Review Date: 09/2019

Louisiana

Human Growth Hormone

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Coding

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Code Type	Code
CPT	No codes
HCPCS	J2941, S9558
ICD-10 Diagnosis	All related diagnoses codes

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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