Medical Policy

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Title: Human Growth Hormone

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Populations	Interventions	Comparators	Outcomes
Individuals: • With proven 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 short stature due to Prader Willi syndrome	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

Populations	Interventions	Comparators	Outcomes
Individuals: • With short stature due to chronic renal insufficiency	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 short stature due to Turner syndrome	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 short stature due to Noonan syndrome	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 short stature due to SHOX (short stature homeobox-containing gene) 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 severe burns	Interventions of interest are: • Human growth hormone to treat or to prevent growth delay	Comparators of interest are: • Standard wound care	Relevant outcomes include: • Symptoms • Hospitalizations • Treatment-related morbidity
Individuals: • With AIDS wasting	Interventions of interest are: • Human growth hormone	Comparators of interest are: • Treatment with a different medication	Relevant outcomes include: • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With short bowel syndrome on specialized nutritional support	Interventions of interest are: • Human growth hormone	Comparators of interest are: • Standard care of short bowel syndrome	Relevant outcomes include: • Functional outcomes • Health status measures • Treatment-related morbidity
Individuals: • Who are small for gestational age in childhood	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

Populations	Interventions	Comparators	Outcomes
Individuals: • With altered body habitus related to antiretroviral therapy for HIV infection	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 idiopathic short stature	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 "genetic potential" (i.e., lower than expected height percentiles based on parents' height)	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 precocious puberty	Interventions of interest are: • Human growth hormone plus gonadotropin-releasing hormone	Comparators of interest are: • Gonadotropin-releasing hormone only	Relevant outcomes include: • Functional outcomes • Quality of life • Treatment-related morbidity
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 (FDA) for various indications and is also proposed for various off-label indications, such as cystic fibrosis and treatment of older adults without documented growth hormone deficiency (GHD). This evidence review will focus specifically on various off-label indications to evaluate the net health outcome when human growth hormone is used compared with the standard therapy for these conditions.

OBJECTIVE

The objective of this evidence review is to evaluate the net health outcome when human growth hormone is used to treat various off-label indications compared with the net health outcome achieved by standard therapy for these conditions.

BACKGROUND

Growth Hormone

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 radiotherapy
- Extra-pituitary tumor
- Sarcoidosis and/or other infiltrating disorders
- Idiopathic

Growth hormone deficiency 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 has suggested that there may be increases in cardiovascular disease and overall mortality, but it is less clear whether GHD causes these outcomes.

While human GH is approved by the US Food and Drug Administration (FDA) for various indications (see Table 1), this review will focus only on select off-label indications for human GH.

Outcome Measures in Growth Hormone Research

The most common outcome measure reported in GH research is a 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 evidence review, changes in other outcome measures, (eg, functional status, quality of life, disease-specific clinical outcomes) are necessary to demonstrate an improvement in health outcomes.

REGULATORY STATUS

Several formulations of human GH have received FDA approval for various indications (Table 1). This evidence review has been modified as of September 2024 to focus only on select off-label indications. Table 2 provides a summary of recognized on-label uses and supporting references, previously included in the evidence review. These indications will not be addressed further within the evidence review.

Table 1. U.S. Food and Drug Administration Approved Indications by Product

Indications	Genotropin® (Pfizer)	Humatrope® (Lilly)	Norditropin® (Novo-Nordisk)	Nutropin® (Genentech)	Saizen® (Serono)	Serostim® (Serono)	Zomacton® [a] (Ferring)	Zorbtive® (Serono)	Omnitrope® (Sandoz)	Sogroya® (Novo-Nordisk)	Skytrofa®(Ascendis Pharma)	Ngenla® (Pfizer)
Growth failure, pediatric patients with inadequate endogenous GH	Yes	Yes	Yes	Yes	Yes		Yes		Yes	Yes	Yes	Yes
Replacement therapy in adults with GHD	Yes	Yes	Yes	Yes	Yes		Yes		Yes	Yes	Yes	
Growth failure due to Prader-Willi syndrome	Yes		Yes						Yes			
Growth failure associated with chronic renal insufficiency				Yes								
Short stature due to Turner syndrome (45,XO)	Yes	Yes	Yes	Yes			Yes		Yes			
Short stature in pediatrics patients with Noonan syndrome			Yes									
Short stature in pediatrics patients with *SHOX* deficiency		Yes					Yes					
HIV wasting or cachexia						Yes						
Treatment of short bowel syndrome								Yes				
Children born small for gestational age, who fail to show catch-up growth by age 2 y	Yes	Yes	Yes				Yes		Yes			
Idiopathic short stature, defined by height SDS ≤-2.25 in non-GHD pediatric patients	Yes	Yes	Yes	Yes			Yes		Yes			

GH: growth hormone; GHD: growth hormone deficiency; SDS: standard deviation score; *SHOX*; short stature homeobox-containing gene.
[a] In 2015, FDA approved a name change for Tev-Tropin; Tev-Tropin is now known as Zomacton.

Table 2. U.S. Food and Drug Administration Approved Indications and Supporting References

Indications	Supporting References
Proven GH deficiency	GHD in children: Root et al 1998[1], Reiter et al 2006[2], Thornton et al 2021[3], Maniatis et al 2022 [4], Savendahl et al 2022 [5], GHD in adults: Beauregard et al 2008 [6], Widdowson et al 2008[7], Widdowson et al 2010[8], Xue et al 2013 [9], Barake et al 2014 [10], Hoffman et al 2004 [11], Maison et al 2003 [12], Sesmilo et al 2000 [13], Gotherstrom et al 2001[14], Dutta et al 2022 [15], Ishii et al 2017[16],
Short stature due to Prader Willi syndrome	Frixou et al 2021[17], Luo et al 2021[18], Passone et al 2020[19], Kuppens et al 2016[20],
Short stature due to chronic renal insufficiency	Wu et al 2013[21], Hodson et al 2012[22], Hokken-Koelega et al 1991[23], Hokken-Koelega et al 2000[24],
Short stature due to Turner syndrome	Li et al 2018[25], Baxter et al 2007[26], Juloski et al 2016[27],
Short stature due to Noonan syndrome	Giacomozzi et al 2015[28], MacFarlane et al 2001[29],
Short stature due to *SHOX*	Takeda et al 2010[30], Blum et al 2007[31], Benabbad et al 2017[32], Child et al 2019[33], Bruzzi et al 2023[34],
HIV/AIDS wasting or cachexia	Moyle et al 2004[35], Evans et al 2005[36],

Indications	Supporting References
Short bowel syndrome on specialized nutritional support	Wales et al 2010[37], Scolapio 1999[38], Seguy et al 2003[39], Szkudlarek et al 2000[40],
Individuals who are small for gestational age in childhood	Maiorana and Cianfarani 2009[41], Juul et al 2023[42],
Idiopathic short stature	Bryant et al 2007[43], Deodati and Cianfarani 2011[44], Paltoglou et al 2020[45], Shemesh-Iron et al 2019[46], Ross et al 2004[47], Theunissen et al 2002[48], Downie et al 1996[49],

GH: growth hormone; GHD: growth hormone deficiency; *SHOX*; short stature homeobox-containing gene.

POLICY

TARGET DRUGS

Preferred Growth Hormone	Nonpreferred Growth Hormone *
▪ Genotropin® ▪ Omnitrope®	▪ Humatrope® ▪ Ngenla ▪ Norditropin Flexpro® ▪ Nutropin AQ Nuspin® ▪ Nutropin AQ® ▪ Saizen®, Saizen Click. Easy ▪ Serostim® ▪ Skytrofa ® ▪ Sogroya ▪ Zomacton ▪ Zorbtive® *This list may not be all inclusive

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**
   b. 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

   c. Growth failure as defined by the following age groups:
      i. 0-6 months: <34 cm/year
      ii. 6-12 months: <15 cm/year
      iii. 1-3 years: <12 cm/year
      iv. Over three years to puberty (see definition of puberty below): <5 cm/year
      v. 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:
      i. 0-6 months: <34 cm/year
      ii. 6-12 months: <15 cm/year
      iii. 1 - 3 years: <12 cm/year
      iv. Over three years to puberty (see below definition of puberty): <5 cm/year
      v. 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/1.73m^2 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:
      i. 0-6 months: <34 cm/year
      ii. 6-12 months: <15 cm/year
      iii. 1 – 3 years: <12 cm/year
      iv. Over three years to puberty (see below definition of puberty): <5 cm/year
      v. 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.

7. Prevention of growth delay in children with severe burns (see Policy Guidelines).

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

B. **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.

C. **Documentation**
Documentation needed for predetermination is:
1. Growth charts with at least 3 measurements over at least one year
2. Growth hormone stimulation testing results
3. Other supporting documentation

D. **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.

E. **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 continued 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
    d. AIDS wasting syndrome.
    e. Promotion of wound healing in individuals with severe burns (see Policy Guidelines).
    f. Short bowel syndrome receiving specialized nutritional support in conjunction with optimal management of short bowel syndrome (see Policy Guidelines).

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 IFG-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.
   a. AIDS wasting.
   b. Promotion of wound healing in individuals with severe burns (see Policy Guidelines).
   c. Short bowel syndrome receiving specialized nutritional support in conjunction with optimal management of short bowel syndrome (see Policy Guidelines).

F. **A Nonpreferred Growth Hormone will become a Preferred Growth Hormone:**
   1. When **BOTH** of the following criteria are met:
      a. The individual's medication history indicates use of all the preferred growth hormone (GH) agents **AND**
      b. The individual has documented intolerance, FDA labeled contraindication, or hypersensitivity to all preferred growth hormone (GH) agents.
      c. When there is a product supply shortage of the preferred growth hormone(s), a non-preferred growth hormone will become the preferred product only during the shortage.

G. **Length of Approval** 12 months. Growth hormone therapy approved for life will need continued review for benefits.

POLICY GUIDELINES

A. 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.
B. 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 individuals may be more sensitive to the action of GH therapy and may be more prone to develop adverse reactions.
C. Growth hormone is contraindicated in individuals 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 individuals with Prader-Willi syndrome.

D. Insulin tolerance testing is contraindicated in individuals with cardiovascular disease, cerebrovascular disease, seizure disorders or individuals older than 65 years.
E. 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. Individuals treated with growth hormone must simultaneously be treated with antiviral agents. Therapy is continued until this definition is no longer met.
F. Growth hormone for burn individuals should be limited to those individuals with third-degree burns.
G. Growth hormone for individuals with short bowel syndrome should be limited to individuals 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 requirements. Optimal management may include dietary adjustments, enteral feedings, parenteral nutrition, fluid, and micronutrient supplements.

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.

RATIONALE

The evidence review was created using searches of the PubMed database. The most recent literature update was performed through September 10, 2025.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical uses of the technology in the intended population, and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Safety of Growth Hormone Treatment

Adverse events 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, myalgia, headache, edema, and carpal tunnel syndrome are common. Less

common adverse events include pancreatitis and gynecomastia.[50,51,52,] 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.

Johannsson et al (2022) published long-term observational results from the KIMS cohort of the Pfizer International Metabolic Database.[53,] Mean follow-up among the 15,809 patients treated with Genotropin was 5.3 years. Treatment-related adverse events occurred in 18.8% of patients. The risk of de novo cancer was not increased compared to the general population (standard incidence ratio, 0.92; 95% confidence interval [CI], 0.83 to 1.01) regardless of whether growth hormone deficiency (GHD) was adult-onset or childhood-onset.

Beck-Peccoz et al (2020) evaluated malignancy risk in adults with GHD undergoing long-term treatment with Omnitrope in the ongoing Patients Treated with Omnitrope (PATRO) Adults postmarketing surveillance study.[54,] PATRO Adult included 1293 patients as of July 2018 from 76 sites in 8 European countries; enrollees who received ≥1 dose of Omnitrope were included in the safety population. Of these patients, 33 developed on-study malignancies (2.6%; incidence rate of 7.94 per 1000 patient-years) with tumors occurring after a mean of 79.4 months of GH treatment overall. Seven patients experienced >1 malignancy occurrence (n=41 total malignancies). Of the 33 patients, 3 had no prior medical history of malignancies or tumors. The most commonly occurring malignancies included basal cell carcinoma (n=13), prostate (n=6), breast (n=3), kidney (n=3), and malignant melanoma (n=3) and the majority occurred in patients >50 years of age (35 out of 41 cases). Growth hormone treatment was discontinued following malignancy diagnosis in 15 patients. Backeljauw et al (2022) published results of the analogous PATRO Children study.[55,] Among 294 children enrolled in the United States and 6206 children enrolled internationally, treatment-related adverse events were rare (1.7% of patients in the United States, 7.3% of patients internationally). No cancers were considered related to treatment and no hyperglycemia/diabetes mellitus events were reported.

Thomas-Teinturier et al (2020) assessed the impact of GH treatment on the risk of secondary neoplasm in a French cohort of survivors of childhood cancer treated before 1986 (N=2852).[56,] At a median follow-up of 26 years, 196 survivors were administered GH therapy during childhood or adolescence. A total of 374 patients developed at least 1 secondary neoplasm with 40 of these occurring after GH treatment. Results revealed that GH therapy did not increase the risk of secondary non-meningioma brain tumors (relative risk [RR], 0.6; 95% CI, 0.2 to 1.5; p=.3), secondary non-brain cancer (RR, 0.7; 95% CI, 0.4 to 1.2; p=.2), or meningioma (RR, 1.9; 95% CI, 0.9 to 4; p=.09).

Swerdlow et al (2017) published results from the Safety and Appropriateness of Growth Hormone Treatments in Europe study, which compared the risk of cancer mortality and cancer incidence among patients receiving GH therapy with national population rates.[57,] For the cancer mortality analysis, the cohort consisted of 23,984 patients from 8 European countries. For the cancer incidence analysis, only those patients from countries with highly complete cancer registries (Belgium, Netherlands, Sweden, Switzerland, United Kingdom) were included (n=10,406). Over 50% received GH treatment due to "isolated growth failure," defined as GHD, idiopathic short stature, and prenatal growth failure. Other common diagnoses leading to GH treatment included: Turner syndrome, pituitary hormone deficiency, and central nervous system tumor. For the

cancer mortality cohort, mean follow-up was 17 years, mean age at follow-up was 27 years, and there were 251 cancer deaths. For the cancer incidence cohort, mean follow-up was 15 years, mean age at last follow-up was 26 years, and there were 137 incident cancers. For patients whose initial diagnosis was "isolated growth failure," overall cancer risk was not elevated. For patients whose initial diagnosis was not cancer, neither cancer mortality nor cancer incidence was related to the age of treatment initiation and duration of treatment.

Several publications on the safety of GH therapy have used French registry data and vital statistics. Analysis of long-term mortality after GH treatment was conducted by Carel et al (2012).[58,] 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 (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% 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 versus 0.6 expected.

Poidvin et al (2014) reported on the same data, focusing on the risk of stroke in adulthood among childhood users of GH therapy.[59,] This analysis included 6874 children with idiopathic isolated GHD or short stature; the 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.

Tidblad et al (2021) evaluated the potential association between childhood GH treatment and long-term cardiovascular morbidity via a nationwide population-based cohort study of Swedish patients treated with GH during childhood from January 1985 to December 2010 for GHD, small for gestational age, or idiopathic short stature (n=3408).[60,] Data on outcomes of interest were prospectively collected from January 1985 through December 2014. For each case, 15 controls matched for sex, birth year, and geographical region were randomly selected from the Swedish Total Population Register (N =50,036). The primary outcome was the initial cardiovascular event recorded after the start of follow-up. Results revealed that a total of 1809 cardiovascular events were recorded during follow-up. The crude incidence rates were 25.6 (95% CI, 21.6 to 30.4) events per 10,000 person-years among GH patients and 22.6 (95% CI, 21.5 to 23.7) events per 10,000 person-years among controls. Among male patients and controls, the incidence rates

were similar. However, the rate was higher in female GH patients than in female controls (31.2 events per 10,000 person-years vs. 23.2 events per 10,000 person-years). The authors concluded that GH treatment during childhood was associated with increased risks of cardiovascular events in early adulthood, particularly in women. However, a causal association is not definitively established and the absolute risk remains low.

NONRANDOMIZED STUDIES

SEVERE BURNS

Clinical Context and Therapy Purpose

The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with severe burns.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with severe burns.

Interventions

The therapy being considered is human GH to treat or to prevent growth delay.

Comparators

The following practice is currently being used to treat or prevent growth delay due to severe burns: standard wound care. Typical treatment for severe burns includes skin transplantation and grafting.

Outcomes

The general outcomes of interest are symptoms, hospitalizations, and treatment-related morbidity. Follow-up at 2 years is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

TREATMENT OF SEVERE BURNS

Systematic Reviews

A Cochrane review by Breederveld et al (2012) included RCTs evaluating the impact of GH therapy on the healing rates of burn wounds.[61,] 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 shorter in the GH-treated group than in the placebo group (mean difference [MD], -9.07 days; 95% CI, -4.39 to -13.76 days). Reviewers also performed 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 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 (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).

Randomized Controlled Trials

A RCT by Knox et al (1995) measuring mortality included 54 adult burn patients who survived the first 7 postburn days.[62,] Those patients showing difficulty with wound healing were treated with human GH and compared with those healing at the expected rate with standard therapy. The mortality rate of GH-treated patients was 11% compared with 37% for those not receiving GH (p=.027). Infection rates were similar in both groups.

Singh et al (1998) studied 2 groups of patients (N=22) with comparable third-degree burns; those who received GH had improved wound healing and a lower mortality rate (8% vs. 44%).[63,] A placebo-controlled trial by Losada et al (2002) found no benefit to GH with regard to the length of hospitalization in 24 adults with severe burns.[64,]

Prevention of 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 a significantly increased height in a placebo-controlled, randomized, double-blind trial.[65,] Aili Low et al (2001) also found that GH treatment in severely burned children during hospitalization resulted in significantly greater height velocity during the first 2 years after a burn compared with a similar group of untreated children.[66,]

Section Summary: Severe Burns

For individuals who have severe burns who receive human GH, the evidence includes RCTs and a meta-analysis. The meta-analysis 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.

ALTERED BODY HABITUS RELATED TO ANTIRETROVIRAL THERAPY FOR HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Clinical Context and Therapy Purpose

The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with altered body habitus related to antiretroviral therapy for HIV infection.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with altered body habitus related to antiretroviral therapy for HIV infection.

Interventions

The therapy being considered is human GH.

Comparators

The following practice is currently being used to treat altered body habitus due to antiretroviral therapy for HIV infection: standard care without human GH treatment.

Outcomes

The general outcomes of interest are functional outcomes, QOL, and treatment-related morbidity. Treatment of 40 weeks is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Randomized Controlled Trials

Because high-dose GH has been associated with adverse events relating to inflammation, Lindboe et al (2016) conducted a randomized, double-blind, placebo-controlled trial to test the effect of low-dose GH in the treatment of HIV-infected patients on antiretroviral therapy.[67,] Participants were randomized to GH 0.7 mg/day (n=24) or placebo (n=18) for 40 weeks. The primary outcome was change in inflammation measured by C-reactive protein and soluble urokinase plasminogen activator receptor, both of which increase with inflammation. After 40 weeks, low-dose GH significantly lowered C-reactive protein. Low-dose GH lowered soluble urokinase plasminogen activator receptors as well, but the difference was not statistically significant, even after controlling for age, weight, smoking status, and lipodystrophy.

Case Series
A case series was reported by Wanke et al (1999) who treated 10 HIV-infected patients with fat redistribution syndrome with GH for 3 months.[68,] The authors reported improved waist/hip ratio and mid-thigh circumference.

Section Summary: Altered Body Habitus Related to Antiretroviral Therapy for Human Immunodeficiency Virus Infection
For individuals who have altered body habitus related to antiretroviral therapy for HIV infection who receive human GH, the evidence includes a RCT and case series. The RCT measured the effect of low-dose GH on intermediate outcomes (inflammation markers). 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 due to antiretroviral therapy. Controlled studies reporting relevant outcomes are needed.

CHILDREN WITH "GENETIC POTENTIAL"

Clinical Context and Therapy Purpose
The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with "genetic potential".

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with "genetic potential".

Interventions
The therapy being considered is human GH.

Comparators
The following practice is currently being used to treat children with "genetic potential": standard care without human GH treatment.

Outcomes
The general outcomes of interest are functional outcomes, QOL, and treatment-related morbidity. Due to the lack of relevant data, it is not possible to determine an appropriate window for follow-up.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Clinical Studies
No randomized or nonrandomized studies were identified that have evaluated the efficacy, safety, and/or psychosocial impacts of treating children with "genetic potential" (i.e., children with lower than expected height percentiles based on their parents' height).

Section Summary: Children With "Genetic Potential"
For individuals who have "genetic potential" (ie, lower than expected height percentiles based on parents' height), no clinical trials evaluating GH therapy were identified. There is insufficient evidence to draw conclusions about the use of human GH to treat "genetic potential."

PRECOCIOUS PUBERTY

Clinical Context and Therapy Purpose
The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with precocious puberty.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is children with precocious puberty.

Interventions
The therapy being considered is human GH plus gonadotropin-releasing hormone (GnRH).

Comparators
The following practice is currently being used to treat precocious puberty: GnRH only.

Outcomes
The general outcomes of interest are functional outcomes, QOL, and treatment-related morbidity. Follow-up at 2 years is of interest to monitor outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Systematic Reviews

Liu et al (2016) published a meta-analysis comparing GnRH with the combination therapy of GH plus GnRH for the treatment of females who had idiopathic central precocious puberty.[69,] The literature search, conducted through December 2014, identified 6 RCTs (n=162) and 6 clinical controlled trials (n=247) for inclusion. Risk of bias in the RCTs was assessed using the Cochrane Collaboration checklist. Five of the RCTs were determined to have a moderate risk of bias and 1 trial had a high-risk of bias. The controlled trials were assessed using the Methodological Index for Nonrandomized Studies, based on 12 items, with an ideal global score of 24. Scores on the Methodological Index for Nonrandomized Studies for the 6 controlled trials ranged from 17 to 20 because none of the trials reported blinded outcome evaluation or prospective calculation of study size. Primary outcomes included final height, the difference between final height and targeted height, and height gain. Among the 12 included studies, the age of participants ranged from 4.6 to 12.2 years and treatment with the combination therapy ranged from 6 months to 3 years. One RCT and 4 controlled trials provided data for the meta-analyses. Results showed that patients receiving the combination therapy for at least 1 year experienced significantly greater final height, the difference in final height and targeted height, and height gain compared with those receiving GnRH alone (MD, 2.8 cm; 95% CI, 1.8 to 3.9 cm; MD, 3.9 cm; 95% CI, 3.1 to 4.7 cm; MD, 3.5 cm; 95% CI, 1.0 to 6.0 cm, respectively). When treatment duration was less than 1 year, no significant differences in height outcomes were found.

Randomized Controlled Trials

One RCT compared GnRH analogs alone with GnRH analogs plus GH therapy. This trial, by Tuvemo et al (1999), included 46 girls with precocious puberty.[70,] 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 analogs alone. The absence of final height data limited interpretation of this trial.

Section Summary: Precocious Puberty

For individuals who have precocious puberty who receive human GH plus GnRH, the evidence includes a meta-analysis and a RCT. While the meta-analysis included RCTs and controlled trials, only 1 RCT and 4 controlled trials provided data for the meta-analysis informing final height, the difference in final height and targeted height, and height gain. The meta-analysis reported statistically significant gains of several centimeters for patients who received the combination therapy for at least 1 year compared with patients receiving GnRH alone. However, no studies have reported on the impact of short stature on functional or psychological outcomes in this population.

OLDER ADULTS WITH AGE-RELATED GROWTH HORMONE DEFICIENCY

Clinical Context and Therapy Purpose

The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals who are older adults with age-related GHD.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is older adults with age-related GHD.

Interventions
The therapy being considered is human GH.

Comparators
The following practice is currently being used to treat older adults with age-related GHD: standard care without human GH treatment.

Outcomes
The general outcomes of interest are functional outcomes, QOL, and treatment-related morbidity. Due to the lack of relevant data, it is not possible to determine the window for follow-up.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Systematic Reviews
A TEC Assessment (2001) investigated the use of GH in older adults with age-related GHD and concluded that there was insufficient evidence of efficacy.[71,] It is not possible to prove the 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 With Age-Related Growth Hormone Deficiency
For individuals who are older adults with age-related GHD who receive human GH, the evidence includes a systematic review (TEC Assessment). The TEC Assessment concluded there is a lack of evidence that GH therapy in older adults improves health outcomes. No subsequent controlled studies were identified.

CYSTIC FIBROSIS

Clinical Context and Therapy Purpose
The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with cystic fibrosis (CF).

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with CF.

Interventions
The therapy being considered is human GH.

Comparators
The following practice is currently being used to treat CF: standard care without human GH treatment.

Outcomes
The general outcomes of interest are functional outcomes, QOL, and treatment-related morbidity. Treatment of 1 year is of interest to monitor outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Systematic Reviews
A Cochrane review by Thaker et al (2013) evaluated GH therapy for improving lung function, nutritional status, and QOL in children and young adults with CF.[72,] Reviewers identified 4 RCTs (N=161). All studies used daily subcutaneous injection of human GH as the intervention and included a no treatment or a placebo control group. All trials measured pulmonary function and nutritional status. Due to differences in how outcomes were measured, study findings were not pooled. Across trials, GH improved intermediate outcomes such as height and weight; however, improvements in lung function were inconsistent. No significant changes in QOL or clinical status were detected.

An update to the Cochrane review by Thaker et al was published in 2018.[73,] Eight trials (291 participants) were included in the revision, of which 7 compared standard-dose recombinant human growth hormone (rhGH; approximately 0.3 mg/kg/week) to no treatment, and a 3-arm trial (63 participants) compared placebo, standard-dose rhGH (0.3 mg/kg/week) and high-dose rhGH (0.5 mg/kg/week). Results showed that patients receiving rhGH demonstrated modest improvement in height, weight, and lean body mass between 6 and 12 months, but there was no consistent evidence that rhGH improved lung function, muscle strength, or QOL. A subsequent review in 2021 did not find any new studies to add, and the authors concluded that further randomized trial data is needed to justify routine clinical use.[74,]

Previously, a systematic review by Phung et al (2010) identified 10 controlled trials evaluating GH for treating patients with CF.[75,] 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.

Treatment durations ranged from 4 weeks to 1 year. There were insufficient data to determine the effect of GH on most health outcomes (eg, frequency of intravenous antibiotic treatment, QOL, bone fracture). Data were pooled for a single 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 events per year; 95% CI, -1.98 to -1.26 events per year).

Randomized Controlled Trials

An industry-sponsored, open-label RCT was published by Stalvey et al (2012).[76,] It compared GH therapy with no treatment in prepubertal children with CF younger than 14 years of age. Eligibility criteria included height at or under 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 trial included 68 children; 62 (91%) were included in the efficacy analysis, and all but 1 were included in the safety analysis. The annualized height velocity at month 12 was 8.2 cm/y in the treatment group and 5.3 cm/y in the control group ($p<.001$). The mean height standard deviation score (SDS) in the treatment group was -1.8 at baseline, -1.4 at 12 months, and -1.4 at 18 months versus -1.9 at all 3 time points in the control group. The change in mean height SDS from baseline to 12 months was significantly greater in the treatment than in the control group ($p<.001$). Between months 12 and 18, 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 for most variables (7 of 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 ($p<.005$) and forced vital capacity ($p<.01$). In the treatment group, mean forced expiratory volume in 1 second was 1209 L at baseline, 1434 L at 12 months, and 1467 L at 18 months compared with 1400 L at baseline, 1542 L at 12 months, and 1674 L at 18 months in the control group. From baseline to 12 months, the between-group difference in change in the 6-minute walk distance did not differ significantly (26.3 meters; 95% CI, -44.8 to 97.4 meters). Ten children in the treatment group and 9 in the control group were hospitalized for pulmonary exacerbations during the 12-month trial; the difference between groups was not statistically significant. In general, treatment with GH resulted in statistically significant improvements in height SDS but did not significantly improve clinical outcomes associated with CF.

Section Summary: Cystic Fibrosis

For individuals who have CF who receive human GH, the evidence includes RCTs and systematic reviews. The RCTs were heterogeneous and reported various outcomes. Most of the systematic reviews did not pool results for outcomes such as frequency of intravenous antibiotic treatment, QOL, and bone fracture. The single pooled outcome in 1 systematic review (number of hospitalizations) was significantly lower in patients receiving GH therapy versus no treatment or placebo. Across trials, GH was found to improve intermediate outcomes such as height and weight; however, clinically meaningful outcomes relating to lung function were not consistently improved with GH.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Pediatrics

In 2016, the American Academy of Pediatrics published guidelines on the evaluation and referral of children with signs of early puberty.[77,] The use of gonadotropin-releasing hormone analogs were discussed as treatment options, but growth hormone (GH) as a treatment option was not discussed.

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS

Pediatric Endocrine Society

In 2015, the Pediatric Endocrine Society (PES) published an evidence-based report focusing on the risk of neoplasia in patients receiving growth hormone (GH) therapy.[78,] The report concluded that GH therapy can be administered without concerns about the 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 trade-off between a possible benefit of GH therapy and possible risks of neoplasm.

As an addendum to the 2015 guidelines, Grimberg and Allen (2017), guideline coauthors, published a historical review of the use of GH.[79,] They asserted that although the guidelines did not find an association between GH and neoplasia, the use of GH should not necessarily be expanded. While the use of GH for patients with growth hormone deficiency (GHD) was recommended, evidence gaps persist in the use of GH for other indications such as idiopathic short stature and partial isolated GHD. No off-label indications were addressed.

National Institute of Health and Care Excellence

In 2010, the National Institute of Health and Care Excellence issued guidance on human GH for growth failure in children.[80,] The Institute recommended GH as a possible treatment for children with growth failure with any of the following conditions:

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

There was no mention of its use in off-label indications.

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

Ongoing and Unpublished Clinical Trials
There are no currently, ongoing or unpublished trials that might influence this review as of September 2025.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

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.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
J2941	Injection, somatropin, 1 mg
Q0515	Injection, sermorelin acetate, 1 mcg
S9558	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

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:

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	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

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	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: a. Those Insureds over the age 18 with: • Demonstrated hypothalamic or pituitary disease or injury; and • Laboratory proven growth hormone deficiency 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. 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. 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 that 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,

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	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.
	Updated Rationale section.
	In Coding section: ▪ Under ICD-10 diagnoses, changed effective date to "October 1, 2015".
	Updated References section.
06-23-2015	Updated Description section.
12-08-2015	Updated Description section.
	Updated Rationale section.
	Updated References section.
01-01-2017	Updated Description section.
	In Policy section: ▪ 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.)"

REVISIONS	
	▪ 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: ▪ Added ICD-10 codes: B20, K91.2, P70.4, R62.52, T20.311A-S, T20.312A-S, T20.32XA-S, T20.33XA-S, T20.34XA-S, T20.35XA-S, T20.36XA-S, T20.37XA-S, T20.39XA-S, T22.311A-S, T22.312A-S, T22.321A-S, T22.322A-S, T22.331A-S, T22.332A-S, T22.341A-S, T22.342A-S, T22.351A-S, T22.352A-S, T22.361A-S, T22.362A-S, T22.391A-S, T22.392A-S, T23.311A-S, T23.312A-S, T23.321A-S, T23.322A-S, T23.331A-S, T23.332A-S, T23.341A-S, T23.342A-S, T23.351A-S, T23.352A-S, T23.361A-S, T23.362A-S, T23.371A-S, T23.372A-S, T23.391A-S, T23.392A-S, T24.301A-S, T24.302A-S, T24.311A-S, T24.312A-S, T24.321A-S, T24.322A-S, T24.331A-S, T24.332A-S, T24.391A-S, T24.392A-S, T25.311A-S, T25.312A-S, T25.321A-S, T25.322A-S, T25.331A-S, T25.332A-S, T25.391A-S, T25.392A-S.
	Updated References 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 m^2 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 m^2 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"
12-20-2017	Updated Description section.
	In Policy section: ▪ Added "A Nonpreferred Growth Hormone will be approved when BOTH of the following are met: 1. The patient's medication history indicates use of the *preferred* growth hormone (GH) agent and 2. The patient has documented intolerance, FDA labeled contraindication, or hypersensitivity to the *preferred* GH agent."
	Updated Rationale section.
	In Coding section: ▪ Added coding bullets. ▪ ICD-9 codes removed.
	Updated References section.

REVISIONS	
12-05-2018	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Removed coding bullets.
	Updated References section.
10-01-2019	In Coding section: ▪ Removed ICD-10 code: Q87.1 ▪ Added ICD-10 codes: Q87.11, Q87.19
01-01-2020	Policy published 01-17-2020. Policy effective 01-01-2020.
	In Title section: ▪ Revised "Pre-Determination of Services" to "Prior Authorization" to accurately reflect terminology.
	In Description section: ▪ Updated the Target Drugs Chart to reflect "Norditropin Flexpro" is the preferred growth hormone effective 01-01-2020. "Omnitrope" is a nonpreferred growth hormone.
10-01- 2020	In Coding Section: • Added ICD-10: N18.31, N18.32 • Removed ICD-10: N18.3
12-02-2021	Updated Description Section
	Updated Policy Section ▪ Changed: "A Nonpreferred Growth Hormone" to read "A Nonpreferred Growth Hormone will become a Preferred Growth Hormone:"
	Updated Rationale Section
	Updated References Section
03-17-2022	Updated Target Drugs Section: Added: Skytrofa to "Nonpreferred Growth Hormone"
02-17-2023	Updated Description Section
	Updated Policy Section ▪ Added Genotropin® as a preferred growth hormone in the TARGET DRUGS box
	Updated Rationale Section
	Updated References Sections
06-13-2023	Updated Policy Section ▪ Section E1b added "continued" to read "Childhood onset of growth hormone deficiency and continued deficiency is demonstrated by GH stimulation retesting during adulthood" ▪ Section F1c added "When there is a product supply shortage of the preferred growth hormone(s), a non-preferred growth hormone will become the preferred product only during the shortage."
	Updated Coding Section ▪ Removed ICD-10 Codes
10-12-2023	Updated Policy Section ▪ In the Target Drugs Box added: "Ngenla," "Sogroya," and "*This list may not be all inclusive" under Nonpreferred Growth Hormone section.
11-17-2023	Updated Description Section
	Updated Policy Section ▪ In the Target Drugs Box added: "Omnitrope®" to the Preferred Growth Hormone list and removed it from the Nonpreferred list.
	Update Rationale Section

REVISIONS	
	Updated References Section
Posted 04-05-2024 Effective 05-05-2024	Updated Policy Section ▪ In the Target Drug Box removed "Norditropin Flexpro®" from the preferred list and added "Norditropin Flexpro®" to the Nonpreferred list.
	▪ A Prior Authorization form for Human Growth Hormone was added to the end of the medical policy
01-21-2025	Updated Description Section
	Updated Policy Section ▪ Added to section E. Adult growth Hormone Therapy d. AIDS wasting syndrome. e. Promotion of wound healing in individuals with severe burns (see Policy Guidelines). f. Short bowel syndrome receiving specialized nutritional support in conjunction with optimal management of short bowel syndrome (see Policy Guidelines).
	Updated Policy Guidelines ▪ Removed: Member Contract Language Growth Hormone therapy is covered only under one of the following circumstances: 1. 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. 2. 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. 3. Children, Adolescents and Adults: a. AIDS wasting syndrome b. Short bowel syndrome c. Severe burn individuals
	Updated Rationale Section
	Updated References Section
12-09-2025	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Removed Deleted Code J2940 (eff. 01-01-2026)
	Updated Reference Section
04-14-2026	Removed the Prior Authorization Form from the medical policy.

REFERENCES

1. Root AW, Kemp SF, Rundle AC, et al. Effect of long-term recombinant growth hormone therapy in children--the National Cooperative Growth Study, USA, 1985-1994. J Pediatr Endocrinol Metab. 1998; 11(3): 403-12. PMID 11517956
2. Reiter EO, Price DA, Wilton P, et al. Effect of growth hormone (GH) treatment on the near-final height of 1258 patients with idiopathic GH deficiency: analysis of a large international database. J Clin Endocrinol Metab. Jun 2006; 91(6): 2047-54. PMID 16537676
3. Thornton PS, Maniatis AK, Aghajanova E, et al. Weekly Lonapegsomatropin in Treatment-Naïve Children With Growth Hormone Deficiency: The Phase 3 heiGHt Trial. J Clin Endocrinol Metab. Oct 21 2021; 106(11): 3184-3195. PMID 34272849
4. Maniatis AK, Casella SJ, Nadgir UM, et al. Safety and Efficacy of Lonapegsomatropin in Children With Growth Hormone Deficiency: enliGHten Trial 2-Year Results. J Clin Endocrinol Metab. Jun 16 2022; 107(7): e2680-e2689. PMID 35428884
5. Sävendahl L, Battelino T, Højby Rasmussen M, et al. Effective GH Replacement With Once-weekly Somapacitan vs Daily GH in Children with GHD: 3-year Results From REAL 3. J Clin Endocrinol Metab. Apr 19 2022; 107(5): 1357-1367. PMID 34964458
6. Beauregard C, Utz AL, Schaub AE, et al. Growth hormone decreases visceral fat and improves cardiovascular risk markers in women with hypopituitarism: a randomized, placebo-controlled study. J Clin Endocrinol Metab. Jun 2008; 93(6): 2063-71. PMID 18381581
7. Widdowson WM, Gibney J. The effect of growth hormone replacement on exercise capacity in patients with GH deficiency: a metaanalysis. J Clin Endocrinol Metab. Nov 2008; 93(11): 4413-7. PMID 18697875
8. Widdowson WM, Gibney J. The effect of growth hormone (GH) replacement on muscle strength in patients with GH-deficiency: a meta-analysis. Clin Endocrinol (Oxf). Jun 2010; 72(6): 787-92. PMID 19769614
9. Xue P, Wang Y, Yang J, et al. Effects of growth hormone replacement therapy on bone mineral density in growth hormone deficient adults: a meta-analysis. Int J Endocrinol. 2013; 2013: 216107. PMID 23690770
10. Barake M, Klibanski A, Tritos NA. Effects of recombinant human growth hormone therapy on bone mineral density in adults with growth hormone deficiency: a meta-analysis. J Clin Endocrinol Metab. Mar 2014; 99(3): 852-60. PMID 24423364
11. Hoffman AR, Kuntze JE, Baptista J, et al. Growth hormone (GH) replacement therapy in adult-onset gh deficiency: effects on body composition in men and women in a double-blind, randomized, placebo-controlled trial. J Clin Endocrinol Metab. May 2004; 89(5): 2048-56. PMID 15126520
12. Maison P, Chanson P. Cardiac effects of growth hormone in adults with growth hormone deficiency: a meta-analysis. Circulation. Nov 25 2003; 108(21): 2648-52. PMID 14623813
13. Sesmilo G, Biller BM, Llevadot J, et al. Effects of growth hormone administration on inflammatory and other cardiovascular risk markers in men with growth hormone deficiency. A randomized, controlled clinical trial. Ann Intern Med. Jul 18 2000; 133(2): 111-22. PMID 10896637
14. Götherström G, Svensson J, Koranyi J, et al. A prospective study of 5 years of GH replacement therapy in GH-deficient adults: sustained effects on body composition, bone

mass, and metabolic indices. J Clin Endocrinol Metab. Oct 2001; 86(10): 4657-65. PMID 11600522
15. Dutta D, Mahajan K, Kumar M, et al. Efficacy and safety of long-acting growth hormone in adult growth hormone deficiency: A systematic review and meta-analysis. Diabetes Metab Syndr. Feb 2022; 16(2): 102421. PMID 35158212
16. Ishii H, Shimatsu A, Nishinaga H, et al. Assessment of quality of life on 4-year growth hormone therapy in Japanese patients with adult growth hormone deficiency: A post-marketing, multicenter, observational study. Growth Horm IGF Res. Oct 2017; 36: 36-43. PMID 28923784
17. Frixou M, Vlek D, Lucas-Herald AK, et al. The use of growth hormone therapy in adults with Prader-Willi syndrome: A systematic review. Clin Endocrinol (Oxf). Apr 2021; 94(4): 645-655. PMID 33296095
18. Luo Y, Zheng Z, Yang Y, et al. Effects of growth hormone on cognitive, motor, and behavioral development in Prader-Willi syndrome children: a meta-analysis of randomized controlled trials. Endocrine. Feb 2021; 71(2): 321-330. PMID 33222122
19. Passone CGB, Franco RR, Ito SS, et al. Growth hormone treatment in Prader-Willi syndrome patients: systematic review and meta-analysis. BMJ Paediatr Open. 2020; 4(1): e000630. PMID 32411831
20. Kuppens RJ, Bakker NE, Siemensma EP, et al. Beneficial Effects of GH in Young Adults With Prader-Willi Syndrome: A 2-Year Crossover Trial. J Clin Endocrinol Metab. Nov 2016; 101(11): 4110-4116. PMID 27552545
21. Wu Y, Cheng W, Yang XD, et al. Growth hormone improves growth in pediatric renal transplant recipients--a systemic review and meta-analysis of randomized controlled trials. Pediatr Nephrol. Jan 2013; 28(1): 129-33. PMID 22660958
22. Hodson EM, Willis NS, Craig JC. Growth hormone for children with chronic kidney disease. Cochrane Database Syst Rev. Feb 15 2012; 2012(2): CD003264. PMID 22336787
23. Hokken-Koelega AC, Stijnen T, de Muinck Keizer-Schrama SM, et al. Placebo-controlled, double-blind, cross-over trial of growth hormone treatment in prepubertal children with chronic renal failure. Lancet. Sep 07 1991; 338(8767): 585-90. PMID 1715501
24. Hokken-Koelega A, Mulder P, De Jong R, et al. Long-term effects of growth hormone treatment on growth and puberty in patients with chronic renal insufficiency. Pediatr Nephrol. Jul 2000; 14(7): 701-6. PMID 10912546
25. Li P, Cheng F, Xiu L. Height outcome of the recombinant human growth hormone treatment in Turner syndrome: a meta-analysis. Endocr Connect. Apr 2018; 7(4): 573-583. PMID 29581156
26. Baxter L, Bryant J, Cave CB, et al. Recombinant growth hormone for children and adolescents with Turner syndrome. Cochrane Database Syst Rev. Jan 24 2007; (1): CD003887. PMID 17253498
27. Juloski J, Dumančić J, Šćepan I, et al. Growth hormone positive effects on craniofacial complex in Turner syndrome. Arch Oral Biol. Nov 2016; 71: 10-15. PMID 27372203
28. Giacomozzi C, Deodati A, Shaikh MG, et al. The impact of growth hormone therapy on adult height in noonan syndrome: a systematic review. Horm Res Paediatr. 2015; 83(3): 167-76. PMID 25721697
29. MacFarlane CE, Brown DC, Johnston LB, et al. Growth hormone therapy and growth in children with Noonan's syndrome: results of 3 years' follow-up. J Clin Endocrinol Metab. May 2001; 86(5): 1953-6. PMID 11344190

30. Takeda A, Cooper K, Bird A, et al. Recombinant human growth hormone for the treatment of growth disorders in children: a systematic review and economic evaluation. Health Technol Assess. Sep 2010; 14(42): 1-209, iii-iv. PMID 20849734
31. Blum WF, Crowe BJ, Quigley CA, et al. Growth hormone is effective in treatment of short stature associated with short stature homeobox-containing gene deficiency: Two-year results of a randomized, controlled, multicenter trial. J Clin Endocrinol Metab. Jan 2007; 92(1): 219-28. PMID 17047016
32. Benabbad I, Rosilio M, Child CJ, et al. Safety Outcomes and Near-Adult Height Gain of Growth Hormone-Treated Children with SHOX Deficiency: Data from an Observational Study and a Clinical Trial. Horm Res Paediatr. 2017; 87(1): 42-50. PMID 28002818
33. Child CJ, Zimmermann AG, Chrousos GP, et al. Safety Outcomes During Pediatric GH Therapy: Final Results From the Prospective GeNeSIS Observational Program. J Clin Endocrinol Metab. Feb 01 2019; 104(2): 379-389. PMID 30219920
34. Bruzzi P, Vannelli S, Scarano E, et al. Real-life long-term efficacy and safety of recombinant human growth hormone therapy in children with short stature homeobox-containing deficiency. Endocr Connect. Jul 01 2023; 12(7). PMID 37014306
35. Moyle GJ, Schoelles K, Fahrbach K, et al. Efficacy of selected treatments of HIV wasting: a systematic review and meta-analysis. J Acquir Immune Defic Syndr. Dec 01 2004; 37 Suppl 5: S262-76. PMID 15722869
36. Evans WJ, Kotler DP, Staszewski S, et al. Effect of recombinant human growth hormone on exercise capacity in patients with HIV-associated wasting on HAART. AIDS Read. Jun 2005; 15(6): 301-3, 306-8, 310, 314. PMID 15962453
37. Wales PW, Nasr A, de Silva N, et al. Human growth hormone and glutamine for patients with short bowel syndrome. Cochrane Database Syst Rev. Jun 16 2010; (6): CD006321. PMID 20556765
38. Scolapio JS. Effect of growth hormone, glutamine, and diet on body composition in short bowel syndrome: a randomized, controlled study. JPEN J Parenter Enteral Nutr. 1999; 23(6): 309-12; discussion 312-3. PMID 10574477
39. Seguy D, Vahedi K, Kapel N, et al. Low-dose growth hormone in adult home parenteral nutrition-dependent short bowel syndrome patients: a positive study. Gastroenterology. Feb 2003; 124(2): 293-302. PMID 12557135
40. Szkudlarek J, Jeppesen PB, Mortensen PB. Effect of high dose growth hormone with glutamine and no change in diet on intestinal absorption in short bowel patients: a randomised, double blind, crossover, placebo controlled study. Gut. Aug 2000; 47(2): 199-205. PMID 10896910
41. Maiorana A, Cianfarani S. Impact of growth hormone therapy on adult height of children born small for gestational age. Pediatrics. Sep 2009; 124(3): e519-31. PMID 19706577
42. Juul A, Backeljauw P, Højby M, et al. Somapacitan in children born small for gestational age: a multi-centre, open-label, controlled phase 2 study. Eur J Endocrinol. Jan 10 2023; 188(1). PMID 36651161
43. Bryant J, Baxter L, Cave CB, et al. Recombinant growth hormone for idiopathic short stature in children and adolescents. Cochrane Database Syst Rev. Jul 18 2007; (3): CD004440. PMID 17636758
44. Deodati A, Cianfarani S. Impact of growth hormone therapy on adult height of children with idiopathic short stature: systematic review. BMJ. Mar 11 2011; 342: c7157. PMID 21398350

45. Paltoglou G, Dimitropoulos I, Kourlaba G, et al. The effect of treatment with recombinant human growth hormone (rhGH) on linear growth and adult height in children with idiopathic short stature (ISS): a systematic review and meta-analysis. J Pediatr Endocrinol Metab. Dec 16 2020; 33(12): 1577-1588. PMID 33035189
46. Shemesh-Iron M, Lazar L, Lebenthal Y, et al. Growth hormone therapy and short stature-related distress: A randomized placebo-controlled trial. Clin Endocrinol (Oxf). May 2019; 90(5): 690-701. PMID 30721549
47. Ross JL, Sandberg DE, Rose SR, et al. Psychological adaptation in children with idiopathic short stature treated with growth hormone or placebo. J Clin Endocrinol Metab. Oct 2004; 89(10): 4873-8. PMID 15472178
48. Theunissen NC, Kamp GA, Koopman HM, et al. Quality of life and self-esteem in children treated for idiopathic short stature. J Pediatr. May 2002; 140(5): 507-15. PMID 12032514
49. Downie AB, Mulligan J, McCaughey ES, et al. Psychological response to growth hormone treatment in short normal children. Arch Dis Child. Jul 1996; 75(1): 32-5. PMID 8813867
50. Blethen SL, Allen DB, Graves D, et al. Safety of recombinant deoxyribonucleic acid-derived growth hormone: The National Cooperative Growth Study experience. J Clin Endocrinol Metab. May 1996; 81(5): 1704-10. PMID 8626820
51. Critical evaluation of the safety of recombinant human growth hormone administration: statement from the Growth Hormone Research Society. J Clin Endocrinol Metab. May 2001; 86(5): 1868-70. PMID 11344173
52. Höybye C, Beck-Peccoz P, Murray RD, et al. Safety and effectiveness of replacement with biosimilar growth hormone in adults with growth hormone deficiency: results from an international, post-marketing surveillance study (PATRO Adults). Pituitary. Aug 2021; 24(4): 622-629. PMID 33742320
53. Johannsson G, Touraine P, Feldt-Rasmussen U, et al. Long-term Safety of Growth Hormone in Adults With Growth Hormone Deficiency: Overview of 15 809 GH-Treated Patients. J Clin Endocrinol Metab. Jun 16 2022; 107(7): 1906-1919. PMID 35368070
54. Beck-Peccoz P, Höybye C, Murray RD, et al. Malignancy risk in adults with growth hormone deficiency undergoing long-term treatment with biosimilar somatropin (Omnitrope ®): data from the PATRO Adults study. Ther Adv Endocrinol Metab. 2020; 11: 2042018820943377. PMID 32973992
55. Backeljauw P, Kanumakala S, Loche S, et al. Safety and effectiveness of Omnitrope ® (somatropin) in PATRO Children: a multi-center, post-marketing surveillance study comparison of US and international cohort data. Eur J Pediatr. Jun 2022; 181(6): 2367-2378. PMID 35275291
56. Thomas-Teinturier C, Oliver-Petit I, Pacquement H, et al. Influence of growth hormone therapy on the occurrence of a second neoplasm in survivors of childhood cancer. Eur J Endocrinol. Oct 2020; 183(4): 471-480. PMID 32738133
57. Swerdlow AJ, Cooke R, Beckers D, et al. Cancer Risks in Patients Treated With Growth Hormone in Childhood: The SAGhE European Cohort Study. J Clin Endocrinol Metab. May 01 2017; 102(5): 1661-1672. PMID 28187225
58. Carel JC, Ecosse E, Landier F, et al. Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of the French SAGhE study. J Clin Endocrinol Metab. Feb 2012; 97(2): 416-25. PMID 22238382

59. Poidvin A, Touzé E, Ecosse E, et al. Growth hormone treatment for childhood short stature and risk of stroke in early adulthood. Neurology. Aug 26 2014; 83(9): 780-6. PMID 25122206
60. Tidblad A, Bottai M, Kieler H, et al. Association of Childhood Growth Hormone Treatment With Long-term Cardiovascular Morbidity. JAMA Pediatr. Feb 01 2021; 175(2): e205199. PMID 33346824
61. Breederveld RS, Tuinebreijer WE. Recombinant human growth hormone for treating burns and donor sites. Cochrane Database Syst Rev. Dec 12 2012; 12: CD008990. PMID 23235668
62. Knox J, Demling R, Wilmore D, et al. Increased survival after major thermal injury: the effect of growth hormone therapy in adults. J Trauma. Sep 1995; 39(3): 526-30; discussion 530-2. PMID 7473919
63. Singh KP, Prasad R, Chari PS, et al. Effect of growth hormone therapy in burn patients on conservative treatment. Burns. Dec 1998; 24(8): 733-8. PMID 9915674
64. Losada F, García-Luna PP, Gómez-Cía T, et al. Effects of human recombinant growth hormone on donor-site healing in burned adults. World J Surg. Jan 2002; 26(1): 2-8. PMID 11898025
65. Hart DW, Herndon DN, Klein G, et al. Attenuation of posttraumatic muscle catabolism and osteopenia by long-term growth hormone therapy. Ann Surg. Jun 2001; 233(6): 827-34. PMID 11371741
66. Aili Low JF, Barrow RE, Mittendorfer B, et al. The effect of short-term growth hormone treatment on growth and energy expenditure in burned children. Burns. Aug 2001; 27(5): 447-52. PMID 11451596
67. Lindboe JB, Langkilde A, Eugen-Olsen J, et al. Low-dose growth hormone therapy reduces inflammation in HIV-infected patients: a randomized placebo-controlled study. Infect Dis (Lond). 2016; 48(11-12): 829-37. PMID 27417288
68. Wanke C, Gerrior J, Kantaros J, et al. Recombinant human growth hormone improves the fat redistribution syndrome (lipodystrophy) in patients with HIV. AIDS. Oct 22 1999; 13(15): 2099-103. PMID 10546863
69. Liu S, Liu Q, Cheng X, et al. Effects and safety of combination therapy with gonadotropin-releasing hormone analogue and growth hormone in girls with idiopathic central precocious puberty: a meta-analysis. J Endocrinol Invest. Oct 2016; 39(10): 1167-78. PMID 27225286
70. Tuvemo T, Gustafsson J, Proos LA. Growth hormone treatment during suppression of early puberty in adopted girls. Swedish Growth Hormone Advisory Group. Acta Paediatr. Sep 1999; 88(9): 928-32. PMID 10519330
71. Blue Cross Blue Shield Association Technology Evaluation Center (TEC). Recombinent Human Growth Hormone (GH) Therapy in Adults with Age-Related GH Deficiency. TEC Assessment. 2001;Tab 11. PMID
72. Thaker V, Haagensen AL, Carter B, et al. Recombinant growth hormone therapy for cystic fibrosis in children and young adults. Cochrane Database Syst Rev. Jun 05 2013; 6(6): CD008901. PMID 23737090
73. Thaker V, Carter B, Putman M. Recombinant growth hormone therapy for cystic fibrosis in children and young adults. Cochrane Database Syst Rev. Dec 17 2018; 12(12): CD008901. PMID 30557452

74. Thaker V, Carter B, Putman M. Recombinant growth hormone therapy for cystic fibrosis in children and young adults. Cochrane Database Syst Rev. Aug 23 2021; 8(8): CD008901. PMID 34424546
75. Phung OJ, Coleman CI, Baker EL, et al. Recombinant human growth hormone in the treatment of patients with cystic fibrosis. Pediatrics. Nov 2010; 126(5): e1211-26. PMID 20921071
76. Stalvey MS, Anbar RD, Konstan MW, et al. A multi-center controlled trial of growth hormone treatment in children with cystic fibrosis. Pediatr Pulmonol. Mar 2012; 47(3): 252-63. PMID 21905270
77. Kaplowitz P, Bloch C, Sills IN, et al. Evaluation and Referral of Children With Signs of Early Puberty. Pediatrics. Jan 2016; 137(1). PMID 26668298
78. Raman S, Grimberg A, Waguespack SG, et al. Risk of Neoplasia in Pediatric Patients Receiving Growth Hormone Therapy--A Report From the Pediatric Endocrine Society Drug and Therapeutics Committee. J Clin Endocrinol Metab. Jun 2015; 100(6): 2192-203. PMID 25839904
79. Grimberg A, Allen DB. Growth hormone treatment for growth hormone deficiency and idiopathic short stature: new guidelines shaped by the presence and absence of evidence. Curr Opin Pediatr. Aug 2017; 29(4): 466-471. PMID 28525404
80. National Institute for Health and Care Excellence (NICE). Human growth hormone (somatropin) for growth failure in children [TA188]. 2010; https://www.nice.org.uk/guidance/ta188. Accessed September 10, 2025.

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.
4. Blue Cross and Blue Shield of Kansas Medical Consultant, Practicing Board Certified Pediatric Endocrinologist (340), March 27, 2007; 9/24/2007 and 10/03/2007.
5. National Medical Consultant, Board Certified in Pediatric Endocrinology, Case 10758695, 8/27/2007.
6. National Medical Consultant, Board Certified in Pediatric Endocrinology (335), 2/15/2008, 2/26/2008, and 5/28/2008.
7. Blue Cross and Blue Shield of Kansas Member Contract, January 2008.
8. C&A Medical Consultant, Board Certified in Pediatric Endocrinology (316), 7/16/10 and 8/16/2010.
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, Family Practice Liaison Committee CB, October 2013

Human Growth Hormone
1. Blue Cross and Blue Shield of Kansas Internal Medicine Liaison Committee, August 2014; June 2017, February 2022, June 2023.
2. Blue Cross and Blue Shield of Kansas Pediatric Liaison Committee, July 2014; May 2017; January 2022, May 2023, May 2024, April 2025.