Medical Policy

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Title: Human Growth Hormone

Prior Authorization of services may be required by Member's Contract.

Prior Authorization Form:
BCBSKS reviews the Prior Authorization requests
http://www.bcbsks.com/CustomerService/Forms/pdf/15-811_Growth_Hormone_PA.pdf

Link to Drug List (Formulary):
http://www.bcbsks.com/drugs/

Professional / Institutional
Original Effective Date: February 4, 1986 / August 18, 2008
Latest Review Date: November 17, 2023
Current Effective Date: November 17, 2023

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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

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Populations	Interventions	Comparators	Outcomes
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
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

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Populations	Interventions	Comparators	Outcomes
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
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).

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OBJECTIVE

The objective of this evidence review is to evaluate the net health outcome when human growth hormone is used to treat various U.S. Food and Drug Administration approved and 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.

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

Selection Criteria

These broadened patient selection criteria have remained controversial due to uncertainties in almost every step in the diagnosis and treatment process–selection of patients to be tested, limitations in laboratory testing for GH, establishment of diagnostic cutoffs for normal versus abnormal GH levels, availability of laboratory tests to predict response to GH therapy, changes in growth velocity due to GH therapy, whether resulting final height is significantly improved, and

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whether this improvement is clinically or emotionally significant for the patient. In addition, there are many ethical considerations regarding GH therapy, most prominently appropriate informed consent when the therapy is primarily requested by parents due to their particular psychosocial concerns about height.

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

Outcome Measures in 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 (e.g., 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, (e.g., 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).

In September 2020, the FDA approved the first human GH therapy that adults may take only once a week by injection under the skin - somapacitan (Sogroya®); in 2023, the indication was expanded to include pediatric patients 2.5 years of age and older. In August 2021, lonapegsomatropin-tcgd (Skytrofa®) was approved for the once-weekly treatment of pediatric patients (≥1 year of age) who weigh at least 11.5 kg and have growth failure due to inadequate secretion of endogenous GH. In 2023, somatrogon-ghla (Ngenla®) was approved for the once-weekly treatment of pediatric patients 3 years of age and older who have growth failure due to inadequate secretion of endogenous GH.

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Table 1. FDA Approved Indications by Product

Indications	Genotropin® (Pfizer)	Humatrope®(Lilly)	Norditropin® (Novo-Nordisk)	Nutropin® (Genentech)	Saizen® (Serono)	Zomacton® (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		
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											
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			
Idiopathic short stature, defined by height SDS ≤-2.25 in non-GHD pediatric patients	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.

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POLICY

TARGET DRUGS

Preferred Growth Hormone	Nonpreferred Growth Hormone *
▪ Norditropin Flexpro® ▪ Genotropin® ▪ Omnitrope® ▪	▪ Humatrope® ▪ Ngenla ▪ 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

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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).

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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

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

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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

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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.

H. 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

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 has been updated regularly with searches of the PubMed database. The most recent literature update was performed through August 18, 2023.

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.

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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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Safety of Growth Hormone Treatment

Adverse events can occur with growth hormone (GH) treatment. In children, increased rates of skeletal problems (e.g., 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.[1,2,3,] 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.[4,] 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.[5,] 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

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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.[6,] 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).[7,] 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.[8,] 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).[9,] 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

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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.[10,] 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 (i.e., 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).[11,] 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.

According to drug prescribing information, GH therapy use has been associated with sudden death in children with Prader-Willi syndrome.[12,13,] These deaths occurred among children who were severely obese or had severe respiratory impairment; these characteristics are now considered contraindications to GH treatment in patients with Prader-Willi syndrome.

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 patients with proven GHD.

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Populations
The relevant population of interest is individuals with proven GHD.

Interventions
The therapy being considered is human GH.

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

Outcomes
The general outcomes of interest are functional outcomes, QOL, and treatment-related morbidity. Follow-up at 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

Growth Hormone Deficiency in Children
In children with GHD, treatment has been found to increase growth velocity and final height. Root et al (1998) followed approximately 20,000 children for 9 years as part of the National Cooperative Growth Study.[14,] Growth velocity improved compared with pretreatment values, and this improvement was maintained for at least 4 years. For children treated for at least 7 years, improvements in the mean height standard deviation score (SDS) ranged from 1.3 to 2.5, depending on the specific underlying condition. If treatment is started at an early age, most children can achieve a final height close to that expected from a parental height. In a study of 1258 patients in the Pfizer International Growth Database, Reiter et al (2006) found the standard deviation (SD) for differences between the final height achieved and the midrange of predicted height from parental values ranged between -0.6 and +0.2, depending on the specific underlying condition.[15,]

Once-weekly lonapegsomatropin in children was compared to daily somatropin in children with GHD in an open-label randomized trial.[16,17,] At the end of 2-year follow-up, height was improved by 1.37 to 2.89 SDS with lonapegsomatropin and 1.52 to 3.0 SDS with daily somatropin. At 104 weeks, bone age was minimally advanced relative to chronological age. Similarly, once-weekly somapacitan was compared to daily somatropin in children with GHD in a multicenter RCT. [18,] After 3 years of follow-up, the mean height SDS was similar between treatment groups.

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Growth Hormone Deficiency in Adults

In adults with GHD, evidence from RCTs has shown that treatment leads to increases in lean body mass and decreases in body fat.[19,]

Systematic Reviews

Meta-analyses of RCTs have shown evidence for increases in muscle strength and exercise capacity, although these findings were not robust across all studies.[20,21,] There is also evidence from meta-analyses that GH therapy is associated with increased bone mineral density (BMD) in adults with GHD.[22,23,] For example, a meta-analysis by Barake et al (2014) identified 9 placebo-controlled randomized trials with at least 1-year follow-up on the effect of daily GH therapy on BMD.[23,] Analysis of RCT data found a statistically significant increase in BMD of the lumbar spine and femoral neck in patients with GHD who received GH therapy for more than 2 months. Change in BMD ranged from 1% to 5% at the spine and 0.6% to 4% at the femoral neck. A limitation of the Barake et al (2014) analysis is that data were not available on fracture rates, a clinically important outcome. The evidence on other outcomes (e.g., QOL, lipid profiles, cardiovascular disease, total mortality) has been inconsistent and insufficient to determine whether these outcomes improved with treatment.[24,25,26,27,] A meta-analysis of 5 studies (N=648) that compared long-acting GH and short-acting GH in adults with GHD found similar changes in lean mass, fat mass, and adverse events (including headache, arthralgia, and new-onset diabetes) between formulations.[28,]

Observational Studies

Ishii et al (2017) published an industry-funded, multicenter, observational study of GH therapy for adults with GHD.[29,] One hundred sixty-one patients were eligible for QOL analysis using the Adult Hypopituitarism Questionnaire (AHQ). For male and female patients combined, AHQ scores were improved from baseline in both psycho-social and physical domains. Women had significantly lower AHQ scores than men throughout, however, the net changes in AHQ scores did not differ significantly between men and women (psycho-social domain: 4.90 vs. 4.36; p=.833; physical domain: 5.04 vs. 2.29; p=.213, respectively), despite an increase in GH dose such that insulin-like growth factor-1 (IGF-1) levels for women reached that of men. The study was limited due to loss of follow-up, data collection being on patient recall, the observational design, and lack of a control group.

Section Summary: Growth Hormone Deficiency in Children and Adults

For individuals who have proven GHD who receive human GH, the evidence includes RCTs, large observational studies, and meta-analyses. Studies have found that, for patients with documented GHD and clinical manifestations such as short stature, GH replacement improves growth velocity and final height achieved. In addition, studies have shown that GH therapy can ameliorate the secondary manifestations of GHD such as an increase in lean muscle mass and BMD seen primarily in older children and adults.

Short Stature Due to Prader-Willi Syndrome

Prader-Willi syndrome is a rare neurodevelopmental disorder characterized by muscular hypotonia, hypogonadism, short stature, obesity, psychomotor delay, neurobehavioral abnormalities, and cognitive impairment. Most children with Prader-Willi syndrome have hypothalamic dysfunction and are GH-deficient. The value of testing for GHD before treatment in these patients is questionable. None of the clinical studies selected patients for treatment based

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on the presence or absence of GHD, nor were results reported separately for those with or without GHD. Information from the product label indicates that the height SDS for children with Prader-Willi syndrome in the clinical studies was -1.6 or less (height was in the 10th percentile or lower).

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 short stature due to Prader-Willi syndrome.

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

Populations
The relevant population of interest is children with short stature due to Prader-Willi syndrome.

Interventions
The therapy being considered is human GH.

Comparators
The following practice is currently being used to treat Prader-Willi syndrome: standard care without human GH treatment.

Outcomes
The general outcomes of interest are functional outcomes, QOL, and treatment-related morbidity. Follow-up at 8 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
Frixou et al (2021) completed a systematic review of 20 trials that evaluated the effects of GH in adults with Prader-Willi syndrome, primarily focusing on effects on body composition, bone, and cardiovascular health.[30,] The included studies evaluated 424 subjects (51% male) with Prader-Willi syndrome; however, it is important to note that 60 subjects were recruited to more than 1 study, leaving 364 unique enrollees. The median (range) dose of GH administered in the studies was approximately 0.8 mg/day (0.5 to 1.0 mg/day) with a median duration of treatment of 1 year and median length of follow-up of 2 years. Overall, results revealed no differences in body mass index with GH therapy, although 2 studies noted an increased body mass index after GH treatment discontinuation. Statistically significant increases in lean body mass and decreases in

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percentage fat mass were seen with therapy. Inconsistent effects of GH on cholesterol and echocardiography parameters were also seen across studies. No differences in BMD were reported. Growth hormone therapy was well tolerated in adults with Prader-Willi syndrome; however, further data are needed to evaluate the effects of GH on bone and cardiovascular health.

Luo et al (2021) performed a meta-analysis of 10 RCTs (N=302) that evaluated the effects of GH on cognitive, motor, and behavioral development in children with Prader-Willi syndrome.[31,] Results revealed no significant differences in cognitive performance (data from 6 RCTs) or objective assessments of behavioral development (data from 2 RCTs) between the GH treatment group and controls (p=.197 and p=.53, respectively). However, a significant improvement in motor development with GH therapy compared to control treatment (p<.001) was observed in data from 5 RCTs.

Passone et al (2020) published a systematic review with meta-analysis evaluating GH treatment in patients with Prader-Willi syndrome.[32,] Sixteen RCTs and 20 non-randomized trials were included in the review; controls included placebo or no treatment. Among patients enrolled in RCTs, treatment with GH significantly improved height (1.67, SDS; 95% CI, 1.54 to 1.81 SDS; n=322), body mass index z-scores (-0.67, SDS; 95% CI, -0.87 to -0.47 SDS; n=119), fat mass proportion (-6.5%, SDS; 95% CI, -8.46 to -4.54% SDS; n=204), and head circumference (mean difference [MD], 0.55 cm; 95% CI, 0.25 to 0.86 cm; n=114) compared to control. Data regarding cognitive function, behavior, motor development, and QOL could not be pooled. However, improvements in cognition and motor development were demonstrated in small studies.

Randomized Controlled Trials

Other RCTs in children have shown improvements in health outcomes with GH treatment. For example, Kuppens et al (2016) published results from a 2-year crossover, blinded, placebo-controlled, randomized trial designed to investigate the effects of GH on body composition in young adults with Prader-Willi syndrome who were treated with GH during childhood and had attained adult height.[33,] Patients (N=27) were stratified by sex and body mass index and randomized to GH or placebo injections once daily. After 1 year, the patients received the alternate treatment. Every 3 months, fat mass and lean body mass were measured by dual-energy x-ray absorptiometry. Growth hormone treatment resulted in lower mean fat mass (-17.3%) and higher lean body mass (+3.5%) compared to placebo.

Case Reports

There have been numerous case reports of sudden unexpected death in patients with Prader-Willi syndrome undergoing GH therapy.[34,35,36,]. These deaths occurred among children who were severely obese or had severe respiratory impairment; these characteristics are now considered contraindications to GH treatment in patients with Prader-Willi syndrome. Furthermore, treatment should be discontinued if upper airway obstruction or sleep apnea occurs.[12,13,]

Section Summary: Short Stature due to Prader-Willi Syndrome

For individuals who have short stature due to Prader-Willi syndrome who receive human GH, the evidence includes a systematic review, meta-analyses, a RCT, and case reports. A systematic review, meta-analyses, and a RCT have found improvements in height, body mass index, body composition, head circumference, and motor development in children with Prader-Willi syndrome

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treated with GH. Case reports have found an increased risk of adverse events, including death, in patients with Prader-Willi syndrome who are severely obese or have a severe respiratory impairment; these characteristics are now considered contraindications to GH treatment in patients with Prader-Willi syndrome.

SHORT STATURE DUE TO CHRONIC RENAL INSUFFICIENCY

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 short stature due to chronic renal insufficiency.

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

Populations

The relevant population of interest is individuals with short stature due to chronic renal insufficiency.

Interventions

The therapy being considered is human GH.

Comparators

The following practice is currently being used to treat short stature due to chronic renal insufficiency: standard care without human GH treatment.

Outcomes

The general outcomes of interest are functional outcomes, QOL, and treatment-related morbidity. Follow-up at 9 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

Wu et al (2013) published a systematic review of RCTs evaluating the impact of GH therapy on height outcomes following a renal transplant in children 0 to 18 years of age.[37,] Five trials (N=401) met reviewers' inclusion criteria (RCTs including renal allograft recipients between 0 and 18 years old). Trials were published between 1996 and 2002. A meta-analysis found significantly improved height velocity at the end of a trial in children taking GH compared with a no-treatment

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control group. At the beginning of the year, both groups had a negative height SDS, with no statistically significant differences between groups. After 1 year, the pooled MD in height SDS was 0.68 (95% CI, 0.25 to 1.11 SDS; p=.002) in favor of the GH group. There were no statistically significant differences between groups in the rate of rejection episodes or in renal function.

Previously, Hodson et al (2012) published a Cochrane review of RCTs evaluating GH treatment in children with chronic kidney disease.[38,] To be included in the review, trials needed to include children 18 years of age or younger who were diagnosed with chronic kidney disease and were predialysis, on dialysis, or posttransplant. In addition, trials had to compare GH treatment with placebo, no treatment, or a different GH regimen, and needed to include height outcomes. Seven RCTs with 809 children met reviewers' criteria. Study entry criteria varied (e.g., ranging from <3rd percentile for chronologic age to <50th percentile for chronologic age). Overall, treatment with GH (28 IU/m^2/wk) compared with placebo or no specific therapy resulted in a statistically significant increase in height SDS at 1 year (8 studies; MD, 0.82; SDS; 95% CI, 0.56 to 1.07 SDS). Moreover, a pooled analysis of 7 studies found a significant increase in height velocity at 1 year in the group receiving GH treatment compared with control (MD, 3.88 cm/y; 95% CI, 3.32 to 4.44 cm/y).

Randomized Controlled Trials

An example of an individual RCT is Hokken-Koelega et al (1991), conducted in the Netherlands.[39,] This double-blind, placebo-controlled crossover trial included 20 prepubertal children with severe growth retardation and chronic renal failure. Entry criteria included height velocity less than the 25th percentile for chronologic age. Patients received 6 months of subcutaneous injection of GH (4 IU/m^2/d) before or after 6 months of placebo injection. There was a 2.9 cm greater increase in height velocity per 6 months with GH than with placebo. Long-term follow-up data on children in this and other Dutch RCTs (maximum of 8 years of treatment) were published in 2000.[40,] Growth hormone treatment resulted in significant improvement in the height SDS compared with baseline scores (p<.001). Moreover, the mean height SDS reached the lower end (-2 SDS) of the normal growth chart after 3 years of treatment. Puberty began at a median age within the normal range for girls and boys, GH therapy did not significantly affect parathyroid hormone concentrations, and there were no radiologic signs of renal osteodystrophy.

Section Summary: Short Stature due to Chronic Renal Insufficiency

For individuals who have short stature due to chronic renal insufficiency who receive human GH, the evidence includes RCTs and meta-analyses. Meta-analyses of RCTs have found significantly increased height and height velocity in children with short stature associated with chronic renal insufficiency who are treated with GH therapy compared with other interventions. There were no significant increases in adverse events related to renal function.

SHORT STATURE DUE TO TURNER SYNDROME

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 short stature due to Turner syndrome.

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Populations
The relevant population of interest is individuals with short stature due to Turner syndrome. Short stature is a characteristic of Turner syndrome, although the syndrome is not associated with GHD. Poor growth is evident in utero, and further deceleration occurs during childhood and at adolescence. The mean adult height for those with Turner syndrome is 58 inches (4 feet, 10 inches).

Interventions
The therapy being considered is human GH.

Comparators
The following practice is currently being used to treat short stature due to Turner syndrome: standard care without human GH treatment.

Outcomes
The general outcomes of interest are functional outcomes, QOL, and treatment-related morbidity. Treatment of an average of 6 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
Li et al (2018) conducted a meta-analysis to determine the effect of recombinant human GH treatment on height outcomes in patients with Turner syndrome.[41,] Eleven RCTs (N=1122), published between 1986 and 2011, were identified for the analysis. Compared with controls, there was a significant increase in final height (MD, 7.2 cm; 95% CI, 5.27 to 9.18 cm; p<.001), height SD (standardized MD [SMD], 1.22 cm; 95% CI, 0.88 to 1.56 cm; p<.001), and height velocity (MD, 2.68 cm/y; 95% CI, 2.34 to 3.02 cm/y; p<.001) for patients receiving GH. After 1 year, bone age increased slightly for the GH group (SMD, 0.32 cm/y; 95% CI, 0.1 to 0.54 cm/y; p=.004). The meta-analysis was limited by the small number of available studies and the lack of sufficient data on final height.

A Cochrane review by Baxter et al (2007) identified 4 RCTs (N=365) evaluating GH for treating Turner syndrome.[42,] Studies included children who had not yet achieved final height, received treatment for at least 6 months, and compared GH with placebo or no treatment. Only 1 trial reported final height, so outcomes could not be pooled. A pooled analysis of 2 trials reported that

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short-term growth velocity was greater in treated than in untreated children (MD, 3 cm/y; 95% CI, 2 to 4 cm/y).

Nonrandomized Studies
In addition to short stature, individuals with Turner syndrome also exhibit craniofacial characteristics such as shorter and flattened cranial bases and inclined maxilla and mandible. A cross-sectional study by Juloski et al (2016) compared the craniofacial morphology of 13 patients who had Turner syndrome treated using GH with 13 patients who had Turner syndrome not treated using GH.[43,] Mean age of participants was 17 years. Individuals in the treatment group had received GH for a mean of 5.8 years. Comparisons of lateral cephalometric radiographs showed that GH therapy significantly increased linear measurements, mainly influencing posterior and anterior face height, mandibular height and length, and maxillary length. Angular measurements and facial height ratio did not differ significantly between groups.

Section Summary: Short Stature due to Turner Syndrome
For individuals who have short stature due to Turner syndrome who receive human GH, the evidence includes meta-analyses of RCTs and an observational study. The available data have shown that GH therapy increases height outcomes (e.g., final height, height velocity) and positively affects craniofacial development in children with short stature and craniofacial complex due to Turner syndrome compared to placebo or no treatment.

SHORT STATURE DUE TO NOONAN SYNDROME

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 short stature due to Noonan syndrome.

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

Populations
The relevant population of interest is individuals with short stature due to Noonan syndrome.

Interventions
The therapy being considered is human GH.

Comparators
The following practice is currently being used to treat short stature due to Noonan syndrome: standard care without human GH treatment.

Outcomes
The general outcomes of interest are functional outcomes, QOL, and treatment-related morbidity. Follow-up to 3 years is of interest to monitor outcomes.

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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

Giacomozzi et al (2015) published a systematic review of the literature on the effect of GH therapy on adult height.[44,] Included in the review were studies treating individuals with a diagnosis of Noonan syndrome with no other causes of short stature and a normal karyotype in females. In addition, studies had to follow patients for at least 3 years. Twenty-three studies were identified in a literature search conducted through April 2014, and 6 studies (N=177) met the inclusion criteria; none were RCTs, 1 was controlled, and the rest were prospective or retrospective cohort studies or case reports. To summarize, in the controlled study by MacFarlane et al (2001)[45,], the GH-treated group gained a mean of 3.3 cm more than the untreated group over a 3-year follow-up. Among uncontrolled studies, 2 reported adult height. Mean height SDS was -2.8 (SD, 0.6), and mean adult height SDS was -1.4 (SD, 0.9). Two uncontrolled studies reported near-adult height, which was -2.1 (SD, 0.9). In addition, 2 studies reported a change in height SDS corresponding to 8.6 cm (SD, 5.9). Mean gain in height SDS ranged from 0.6 to 1.4 cm by national standards, and between 0.6 and 2.0 cm by Noonan standards. The data were limited by the paucity of controlled studies and the lack of RCTs.

Section Summary: Short Stature due to Noonan Syndrome

For individuals who have short stature due to Noonan syndrome who receive human GH, the evidence includes a systematic review of controlled and uncontrolled studies. While the studies in the systematic review were generally of low quality and included only 1 trial comparing patients receiving GH with patients receiving no treatment, reviewers found that GH therapy was associated with an increase in height in patients with Noonan syndrome.

SHORT STATURE DUE TO SHORT STATURE HOMEOBOX-CONTAINING GENE 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 patients with short stature due to short stature homeobox-containing gene (*SHOX)* deficiency.

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

Populations

The relevant population of interest is individuals with short stature due to *SHOX* deficiency.

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Interventions
The therapy being considered is human GH.

Comparators
The following practice is currently being used to treat short stature due to *SHOX* deficiency: standard care without human GH treatment.

Outcomes
The general outcomes of interest are functional outcomes, QOL, and treatment-related morbidity. Follow-up to 5 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

Randomized Controlled Trials
A health technology assessment by Takeda et al (2010) assessed GH treatment of growth disorders in children and identified a RCT evaluating GH therapy for children with short stature due to *SHOX* deficiency.[46,] This industry-sponsored, open-label multicenter trial was published by Blum et al (2007).[47,] It included 52 prepubertal children at least 3 years of age who had *SHOX* deficiency. Height requirements were less than the 3rd percentile of the local reference range or less than the 10th percentile with height velocity less than the 25th percentile. Participants were randomized to 2 years of GH treatment (n=27) or usual care (n=25). The primary outcome was first-year height velocity. Fifty-one of 52 patients completed the trial. The first-year height velocity was 8.7 cm/y in the GH therapy group and 5.2 cm/y in the usual care group ($p<.001$). Height gain over the 2-year treatment period was 16.4 cm in the treatment group and 10.5 cm in the usual care group ($p<.001$). No serious adverse events were reported for either group. At the end of the randomized phase, all patients were offered GH.

Nonrandomized Studies
Benabbad et al (2017) published long-term height results and safety data from patients in the Blum et al (2007) RCT (described above) and from a subset of patients with short stature due to *SHOX* deficiency from the Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS).[48,] GeNeSIS was a prospective, multinational, open-label, pediatric surveillance program examining the long-term safety and efficacy of GH. The subset of the GeNeSIS population with *SHOX* deficiency consisted of 521 patients. Forty-nine of the 52 patients in the RCT enrolled in the long-term study. Patients in both studies will be followed until they achieve near-adult (final) height. Final height was defined as attaining 1 of the following criteria: height

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velocity less than 2 cm/y, hand x-ray showing closed epiphyses, or bone age older than 14 years for boys or older than 16 years for girls. At the time of the analysis, 90 patients from GeNeSIS and 28 patients from the RCT reached near-adult height. For the GeNeSIS patients, mean age at GH treatment initiation was 11.0 years, mean age at near-adult height was 15.7 years, and GH treatment duration was 4.4 years. For the RCT patients, mean age at GH initiation was 9.2 years, mean age at near-adult height was 15.5 years, and GH duration was 6.0 years. The most common treatment-emergent adverse events reported in the GeNeSIS patients were: precocious puberty (2.6%) and arthralgia (2.4%). The most common treatment-emergent adverse events reported in the RCT patients were: headache (18.4%) and congenital bowing of long bones (18.4%).

The final results of the GeNeSIS study (mean duration of follow-up, 4.2 years; and mean duration of treatment, 4.9 years) found that the most common treatment-emergent adverse events reported for patients with *SHOX* deficiency continued to be precocious puberty (3%) and arthralgia (2.8%).[49,]

Bruzzi et al (2023) published an Italian retrospective cohort study that reported anthropometric data from children and adolescents (N=117) with *SHOX* deficiency who were treated with GH and followed for up to 4 years.[50,] The study found that growth velocity and height significantly improved during GH treatment. A multiple regression analysis also identified that the main independent predictor factors of height gain were the age at the start of GH treatment (p=.030) and growth velocity during the first year of therapy (p=.008).

Section Summary: Short Stature due to Short Stature Homeobox-Containing Gene Deficiency
For individuals who have short stature due to *SHOX* deficiency who receive human GH, the evidence includes a RCT and long-term observational studies. The RCT found that children with short stature due to *SHOX* deficiency had significantly greater height velocity and height gain after 2 years when treated with GH than with no GH. The long-term studies reported that, after 4 to 6 years of GH treatment, patients with *SHOX* deficiency may attain near-adult height.

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.

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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.[51,] 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 (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.[52,] 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.

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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%).[53,] 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.[54,]

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.[55,] 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.[56,]

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.

ACQUIRED IMMUNODEFICIENCY SYNDROME WASTING

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 AIDS wasting.

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

Populations
The relevant population of interest is individuals with AIDS wasting.

Interventions
The therapy being considered is human GH.

Comparators
The following practice is currently being used to treat AIDS wasting: treatment with different medications.

Outcomes
The general outcomes of interest are functional outcomes, QOL, and treatment-related morbidity. Follow-up at 12 weeks is of interest to monitor outcomes.

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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

Moyle et al (2004) published a systematic review and meta-analysis of controlled and uncontrolled studies on selected treatments of HIV wasting.[57,] To be included, studies had to assess more than 10 patients and have a treatment duration lasting at least 2 weeks. A pooled analysis of 3 studies using GH therapy showed significant increases in lean body mass compared to placebo (MD, 3.1 kg; 95% CI, 2.7 to 3.6 kg). A pooled analysis of 6 studies reporting pre-post lean body mass measurements also showed significant increases following GH treatment (MD, 2.57 kg; 95% CI, 1.4 to 3.7 kg). Lastly, 2 studies found statistically significant improvements in some measurements of QOL after 12 weeks of GH treatment.

Randomized Controlled Trials

A double-blind RCT by Evans et al (2005) included 700 patients with HIV-associated wasting.[58,] Patients were randomized to daily GH, alternate days of GH, or placebo. Patients assigned to daily GH had significantly greater increases in maximum exercise capacity (the primary outcome) than patients assigned to placebo.

Section Summary: Acquired Immunodeficiency Syndrome Wasting

For individuals who have AIDS wasting who receive human GH, the evidence includes a meta-analysis and a RCT. The meta-analysis found significant improvements in lean body mass and QOL with GH therapy versus placebo. A RCT with a large sample size reported a significantly greater increase in exercise capacity with GH than with placebo.

SHORT BOWEL SYNDROME WITH SPECIALIZED NUTRITIONAL SUPPORT

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 short bowel syndrome on specialized nutritional support.

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

Populations

The relevant population of interest is individuals with short bowel syndrome on specialized nutritional support. Short bowel syndrome is experienced by patients who have had 50% or more

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of the small intestine removed. This procedure results in malnourishment because the remaining small intestine is unable to absorb enough water, vitamins, and other nutrients from food.

Interventions
The therapy being considered is human GH.

Comparators
The following practice is currently being used to treat short bowel syndrome: standard of care.

Outcomes
The general outcomes of interest are functional outcomes, health status measures, and treatment-related morbidity. Follow-up at 4 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

Systematic Reviews
A Cochrane review by Wales et al (2010) identified 5 RCTs evaluating GH therapy for treating short bowel syndrome.[59,] Studies evaluated GH with or without glutamine treatment. The primary outcome was change in body weight. A pooled analysis of 3 small trials (n=30) found a statistically significant difference in weight change when patients were treated with GH compared with placebo (MD, 1.7 kg; 95% CI, 0.7 to 2.6 kg; p<.001). Lean body mass, nitrogen absorption, and energy absorption also significantly increased in patients receiving GH therapy compared with controls.

Several published trials have also demonstrated improved intestinal absorption in short bowel syndrome patients receiving parenteral nutrition.[60,61,] However, the Cochrane review and the studies noted that the effects of increased intestinal absorption were limited to the treatment period.[59,61,62,] Specialized clinics may offer intestinal rehabilitation for patients with short bowel syndrome; GH may be a component of this therapy.

Section Summary: Short Bowel Syndrome With Specialized Nutritional Support
For individuals who have short bowel syndrome on specialized nutritional support who receive human GH, the evidence includes RCTs and a meta-analysis. A pooled analysis of 3 RCTs found a significantly greater weight gain during GH therapy compared with placebo in patients with short bowel syndrome; other studies have found improved intestinal absorption during GH therapy in patients with short bowel syndrome receiving parenteral nutrition.

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SMALL FOR GESTATIONAL AGE CHILDREN

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 who are small for gestational age in childhood.

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

Populations
The relevant population of interest is children who are small for gestational age.

Interventions
The therapy being considered is human GH.

Comparators
The following practice is currently being used to treat children small for gestational age: standard care without human GH treatment.

Outcomes
The general outcomes of interest are functional outcomes, QOL, and treatment-related morbidity. Treatment of an average of 7.3 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
A meta-analysis of RCTs evaluating GH treatment for children born small for gestational age was published by Maiorana and Cianfarani (2009).[63,] Four trials (N=391) met selection criteria (birth height or weight <2 SDS, initial height <2 SDS). The GH dose ranged from 33 to 67 µg/kg in the RCTs, and the mean duration of treatment was 7.3 years. The mean adult height in the 4 studies was -1.5 SDS in the treated group and -2.4 SDS in the untreated group. Adult height in the treated group was significantly higher than that of controls (MD, 0.9; SDS [5.7 cm]; p<.0001). There was no difference in adult height between the 33 and 67 µg/kg/d doses. Reviewers noted that it is unclear whether the gain in adult height associated with GH treatment is "of sufficient clinical importance and value to warrant wide-spread treatment of short children born SGA [small for gestational age]…."

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

Randomized Controlled Trial

Juul et al (2023) compared once weekly somapacitan with daily GH in a multicenter, open-label trial that included 62 prepubertal short children born small for gestational age (Table 2).[64,] The main study period was 26 weeks, followed by a 26-week extension, a 4-year safety extension (ongoing), and a 30-day follow-up period. In the first year, the study was designed as a 5-arm, parallel-group study with 3 doses of somapacitan (0.16, 0.20, or 0.24 mg/kg/week) and 2 doses of daily GH (0.035 or 0.067 mg/kg/day). Thereafter, all participants were switched to a single somapacitan dose. The primary outcome, mean annualized height velocity (cm/y) at 26 weeks, was 8.9, 11.0, and 11.3 cm/y for somapacitan 0.16, 0.20, and 0.24 mg/kg/week, respectively, and 10.3 and 11.9 cm/y for daily GH 0.035 and 0.067 mg/kg/day, respectively. A dose-dependent response was confirmed with all treatments and there were no statistically significant differences in height velocity between somapacitan and daily GH (Table 3).

Table 2. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	*Comparator*
Juul (2023)[64,]	US, EU, Asia	38	July 2019 to May 2021	62 prepubertal short children born small for gestational age	Once weekly somapacitan (0.16, 0.20, or 0.24 mg/kg/week)	Daily GH (0.035 or 0.067 mg/kg/day)

GH: growth hormone; RCT: randomized controlled trial.

Table 3. Summary of Key RCT Results

Study	ETD (95% CI) for height velocity (cm/y) at 26 weeks
Jul (2023)[64,]	N=62
Somapacitan 0.16 mg/kg/week vs GH 0.035 mg/kg/day	−1.4 (−3.2 to 0.4)
Somapacitan 0.20 mg/kg/week vs GH 0.035 mg/kg/day	0.7 (−1.1 to 2.5)
Somapacitan 0.20 mg/kg/week vs GH 0.067 mg/kg/day	−0.9 (−2.6 to 0.9)
Somapacitan 0.24 mg/kg/week vs GH 0.067 mg/kg/day	−0.6 (−2.4 to 1.2)

CI: confidence interval; GH: growth hormone; ETD: estimated treatment difference; RCT: randomized controlled trial.

The purpose of the study limitations tables (see Tables 4 and 5) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence

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following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 4. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Juul (2023)[64,]			5. No true comparator (all groups received treatment with GH)		

GH: growth hormone.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 5. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Juul (2023)[64,]		1, 2. Open-label study				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Small for Gestational Age Children

For individuals who are small for gestational age in childhood who receive human GH, the evidence includes a RCT and meta-analysis of RCTs. The RCT compared once-weekly GH therapy (somapacitan) with daily GH therapy in prepubertal short children born small for gestational age (N=62) and found no statistically significant difference in height velocity between treatments at 26 weeks. The meta-analysis found that GH treatment in small for gestational age children

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resulted in significantly greater adult height compared with no treatment; however, the clinical significance of the height difference between the study groups is unclear. There are few data on the psychological or functional outcomes associated with this additional gain in height.

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.[65,] 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

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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.[66,] 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 IDIOPATHIC SHORT STATURE

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 idiopathic short stature.

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

Populations

The relevant population of interest is individuals with idiopathic short stature (without documented GHD or underlying pathology).

Interventions

The therapy being considered is human GH.

Comparators

The following practice is currently being used to treat idiopathic short stature: standard care without human GH treatment.

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;

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- 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

IMPACT ON ADULT HEIGHT

Systematic Reviews

Various meta-analyses have assessed the impact of GH on idiopathic short stature and adult height. Table 2 presents a crosswalk of included trials in these meta-analyses and Table 6 summarizes characteristics of these publications. A Cochrane review by Bryant et al (2007) evaluated GH therapy for idiopathic short stature in children and adolescents.[67,] Ten RCTs met eligibility criteria; 3 studies were placebo-controlled, and the other 7 compared GH therapy with no treatment. Unlike the Deodati and Cianfarani (2011) review (described next), studies were not required to report final adult height. Nine of 10 studies in the Cochrane review were short term and reported intermediate outcomes. A pooled analysis of 3 studies reporting growth velocity at 1 year found a statistically significantly greater growth velocity in treated than in untreated children (Table 8). Five studies reported height SDS, but there was heterogeneity among studies, and findings were not pooled. These data would suggest that GH has an effect on height in children with idiopathic short stature in the short term but that evidence on GH's effects on adult height is limited.

Deodati and Cianfarani (2011) identified 3 RCTs and 7 non-RCTs for inclusion in their systematic review.[68,] Adult height was defined as a growth rate of <1.5 cm/y or bone age of 15 years in females and 16 years in males. The primary efficacy outcome was the difference between groups in adult height, measured as SDS. The investigators considered a MD in height of more than 0.9 SDS (about 6 cm) to be a satisfactory response to GH therapy. Only 1 randomized trial was placebo-controlled, and that trial had a high dropout rate (40% in the treated group, 65% in the placebo group). Table 8 presents results of the analysis. Although GH treatment resulted in a statistically significant increase in adult height in the treated group, according to the *a priori* definition of a satisfactory response (difference, 0.9 SDS), the difference was not clinically significant. Moreover, there was a lack of high-quality, placebo-controlled randomized trials.

Paltoglou et al (2020) also evaluated the effect of GH therapy on linear growth and adult height in children with idiopathic short stature.[69,] This analysis included 21 studies: 10 studies examined the short-term effect of GH on linear growth, while 11 examined the effect of GH treatment on adult height. Overall, 11 of the included trials were randomized (1 trial was double-blind and placebo-controlled) while 10 lacked randomization. Results are presented in Table 8. Overall, children administered GH had a significantly higher height increment at the end of the first and second years of treatment and also achieved significantly higher adult height than the control group. However, the authors acknowledged that their findings indicate "that further studies are required to evaluate the effect of GH treatment in idiopathic short stature" and that "studies of improved quality, larger sample size and properly randomized would be invaluable in elucidating the effect of GH on adult height, as well as the optimal required doses."

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Table 6. Comparison of Trials Included in Systematic Reviews and Meta-Analyses

Study	Paltoglou et al (2020)[69],	Deodati and Cianfarani (2011)[68],	Bryant et al (2007)[67],
Genentech (1989)[70],	●		●
Ackland et al (1990)[71],			●
Cowell et al (1990)[72],			●
Leschek et al (2004)[73],	●	●	●
McCaughey et al (1994)[74],	●		●
Barton et al (1995)[75],			●
Soliman et al (1996)[76],	●		●
Kamp et al (2002)[77],	●		●
Volta et al (1993)[78],	●		●
McCaughey et al (1998)[79],	●	●	●
Albertsson-Wikland et al (2008)[80],	●	●	
Hindmarsh et al (1987)[81],	●		
Wit et al (1989)[82],	●		
Volta et al (1991)[83],	●		
Lanes et al (1995)[84],	●		
Tao et al (2015)[85],	●		
Zadik et al (1992)[86],	●		
Wit et al (1995)[87],	●	●	
Hindmarsh et al (1996)[88],	●	●	
Buchlis et al (1998)[89],	●	●	
Lopez-Siguero et al (2000)[90],	●	●	
Coutant et al (2001)[91],	●	●	
Wit et al (2002)[92],	●	●	
van Gool et al (2010)[93],	●		

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Study	Paltoglou et al (2020)[69,]	Deodati and Cianfarani (2011)[68,]	Bryant et al (2007)[67,]
Lopez-Siguero et al (1996)[94,]		●	

Table 7. Systematic Review and Meta-Analyses Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Bryant et al (2007)[67,]	1980-2006	10	Children with idiopathic short stature and with normal GH secretion, defined as a GH level above 7 µg/L following a stimulation test	633 (18-121)	RCTs	For short-term outcomes: GH had to be given for a minimum of 6 months; for final height outcomes, GH had to be given until final height achieved
Deodati and Cianfarani (2011)[68,]	1985-2010	10	Patients with initial short stature, defined as height >2 SDS below the mean; peak GH responses >10 µg/L; prepubertal state; no previous GH therapy; and no comorbid conditions that would impair growth	592 (14-121)	RCTs (n=3) Non-RCTs (n=7)	Mean duration of therapy was 5.4 yrs
Paltoglou et al (2020)[69,]	1985-2017	21	Children with short stature (height <2 SDS AND no previous GH treatment)	965 (12-335)	RCTs (n=11) Non-RCTs (n=10)	GH treatment for >6 mos

GH: growth hormone; RCT: randomized controlled trial; SDS: standard deviation score.

Table 8. Systematic Review and Meta-Analyses Results

Study	Mean adult height (RCTs)	Mean adult height (non-RCTs)	Growth velocity at 1 year	Height at end of first and second years of treatment	Effect on adult height
Bryant et al (2007)[67,]					
Number of studies			n=3		
WMD (95% CI)			2.48 (2.06 to 2.90)		

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Study	Mean adult height (RCTs)	Mean adult height (non-RCTs)	Growth velocity at 1 year	Height at end of first and second years of treatment	Effect on adult height
Deodati and Cianfarani (2011)[68,]					
Total N	115	477			
SDS GH-treated children	-1.52	-1.7			
SDS untreated children	-2.30	-2.1			
MD (95% CI)	0.65 (0.40 to 0.91 SDS)	0.45 (0.18 to 0.73 SDS)			
p value	<.001	<.001			
Paltoglou et al (2020)[69,]					
Total N				140 (4 studies; 1st yr) 133 (3 studies; 2nd yr)	573 (11 studies)
SMD (95% CI)				0.96 (0.26 to 1.66) 2.37 (1.48 to 3.26)	1.05 (0.68 to 1.42)
p value				<.05 <.001	<.001

CI: confidence interval; GH: growth hormone; MD: mean difference; RCT: randomized controlled trial; SDS: standard deviation score; SMD: standardized mean difference; WMD: weighted mean difference.

Impact on Self-Esteem and Quality of Life

Advocates of GH therapy often cite the potential psychosocial impairments associated with short stature. Several RCTs have investigated this issue and did not find better self-esteem, psychological functioning, or QOL in children treated with GH compared with controls.

Randomized Controlled Trials

Shemesh-Iron et al (2019) published a 1-year blinded RCT and 3-year open-label study evaluating GH therapy in 60 prepubertal boys with idiopathic short stature (mean age, 10 years).[95,] During the blinded phase, patients were randomized to GH therapy (n=40) or placebo (n=20), and in the open-label phase, all patients received GH therapy (n=58). After 1-year, GH therapy significantly improved actual and anticipated adult height perception based on the Silhouette Apperception Test (SAT) (p<.001 and p=.022, respectively) and reduced short stature-related distress based on the Single-Category Implicit Association Test for height (SC-IAT-H; p<.001). After 4-years, GH therapy significantly improved scores on the Rosenberg Self-Esteem Scale (RSES) and SC-IAT-H (p<.001 for both), but there were no significant changes in the Pediatric Quality of Life Inventory (PedsQL) and Child Behavior Checklist (CBCL) scores.

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Ross et al (2004) published findings on psychological adaptation in 68 children with idiopathic short stature without GHD.[96,] Children (mean age, 12.4 years) were randomized to GH therapy (n=37) or placebo (n=31) 3 times per week until height velocity decreased to less than 1.5 cm/y. At baseline and then yearly, parents and children completed several psychological instruments including the CBCL and the Self-Perception Profile. No significant associations were found between attained height SDS or change in height SDS and annual changes in CBCL scores. There were no significant differences between groups on any CBCL summary scales in years 1 and 2, but, in year 4, there were significantly higher scores on the CBCL summary scales in the group receiving GH treatment. There were no significant differences between groups on the Self-Perception Profile at any follow-up point. This trial did not find a correlation between short stature and psychological adaptation or self-concept.

Theunissen et al (2002) in the Netherlands published a trial in which 40 prepubertal children with idiopathic short stature were randomized to GH treatment (n=20) or a control group (n=20).[97,] Parents and children were interviewed at baseline and at 1 and 2 years to obtain information on health-related QOL and children's self-esteem. At the 2-year follow-up, satisfaction with current height was significantly associated with improvement in children's reported health-related QOL, social functioning, and other psychosocial measures. However, satisfaction with height did not differ significantly between the treatment and control groups. The data from this trial did not support the hypothesis that GH treatment improves health-related QOL in children with idiopathic short stature.

Downie et al (1996) examined the behavior of children without documented GHD who were treated with GH due to idiopathic short stature.[98,] Across measures of behavior, including IQ, self-esteem, self-perception, or parental perceptions of competence, there were no significant differences between the control and the treatment groups, either at baseline or after 5 years of GH therapy. The authors concluded that while no psychosocial benefits of GH therapy have been demonstrated, likewise, no documented psychosocial ill effects of GH treatment have been demonstrated.

Section Summary: Children With Idiopathic Short Stature

For individuals who have idiopathic short stature who receive human GH, the evidence includes RCTs and meta-analyses. Meta-analyses have found that GH treatment may increase height gain for children with idiopathic short stature but the difference in height gain may not be clinically significant. Many of the available studies did not follow treated patients long enough to determine the ultimate impact of GH on final adult height. Randomized controlled trials have not consistently found that short stature is associated with psychological problems, contrary to the expectations of some advocates. In addition, the available trials have not reported a correlation between increases in height and improvements in psychological functioning. Moreover, this group of children is otherwise healthy, and there are potential risks to GH therapy in childhood.

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 patients with "genetic potential".

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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" (i.e., 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 patients with precocious puberty.

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

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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.[99,] 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.

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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.[100,] 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 patients 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.

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- 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.[101,] 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 patients 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.

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- 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.[102,] 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.[103,] 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.[104,]

Previously, a systematic review by Phung et al (2010) identified 10 controlled trials evaluating GH for treating patients with CF.[105,] 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 (e.g., 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).[106,] 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 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

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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.[107,] The use of gonadotropin-releasing hormone analogs were discussed as treatment options, but growth hormone (GH) as a treatment option was not discussed.

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American Association of Clinical Endocrinologists
In 2019, the American Association of Clinical Endocrinologists updated its guidelines on GH use in growth hormone deficiency (GHD) adults and patients transitioning from pediatric to adult care.[108,] Evidence-based recommendations included the following:

- GHD is a well-recognized clinical syndrome in adults that is associated with significant comorbidities if untreated
- GH should only be prescribed to patients with clinical features suggestive of adult GHD and biochemically proven evidence of adult GHD
- No data are available to suggest that GH has beneficial effects in treating aging and age-related conditions and the enhancement of sporting performance; therefore, GH treatment was not recommended for any reason other than the well-defined approved uses of the drug
- No evidence exists to support any specific GH product over another.

American Gastroenterological Association
A 2022 American Gastroenterological Association clinical practice update on the management of short bowel syndrome notes that: "The use of recombinant human growth hormone. Has largely been discontinued due to unacceptable side effects and questionable long-term efficacy."[109,]

Endocrine Society
In 2016, the Endocrine Society updated its practice guidelines on adult GHD and included the following recommendations:[110,]

- GH therapy should be offered to patients with proven GHD and no contraindications
- Young adults previously requiring GH therapy for short stature during childhood (isolated GHD with normal pituitary imaging) should be re-evaluated as adults before continuing GH therapy into adulthood
- GH therapy for GHD adults offers significant clinical benefits in body composition and exercise capacity
- GH therapy for GHD adults offers significant clinical benefits in skeletal integrity

Separate Endocrine Society guidelines (2018) make the following recommendations for the treatment of GHD in survivors of childhood cancer:[111,]

- GH therapy should be offered to survivors of childhood cancer with confirmed GHD.
- Patients should be disease-free for 1-year following completion of therapy for cancer before GH therapy is initiated.

Growth Hormone Research Society
The Growth Hormone Research Society (GHRS), Lawson Wilkins Pediatric Endocrine Society, and the European Society for Pediatric Endocrinology Workshop (2008) published a consensus statement on the diagnosis and treatment of children with idiopathic short stature.[112,] The statement indicated that the appropriate height below which GH treatment should be considered ranged from -2 to -3 standard deviation score. The optimal age for treatment was thought to be between 5 years and early puberty. The group noted that psychological issues should be considered (e.g., GH therapy should not be recommended for short children who are unconcerned about stature). The statement also mentioned that "psychological counseling is worthwhile to consider instead of or as an adjunct to hormone treatment."

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The GHRS (2013) issued consensus guidelines on human GH therapy for Prader-Willi syndrome (PWS).[113,] The following recommendations were made:

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

In 2016, results from the Growth Hormone Safety Workshop were published in the *European Journal of Endocrinology*.[114,] The workshop was convened by GHRS and other medical societies. The workshop reappraised the safety of human GH. The position statement concluded:

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

In 2019, the GHRS convened a subsequent Workshop to evaluate the diagnosis and therapy of short stature in children. The Workshop reappraised the safety of human GH and noted:[115,]

- The goal of GH therapy in children with GHD is to replace the deficient GH for growth, metabolism, and well-being
- GH therapy-related adverse effects are uncommon, and data linking rhGH dose to treatment-related adverse events in children are scarce.

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.[116,] 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.[117,] 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.

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In 2016, the PES published guidelines for GH and insulin-like growth factor-1 treatment for children and adolescents with GHD, idiopathic short stature, and primary insulin-like growth factor-1 deficiency.[118,] The guidelines used the GRADE approach (grading of recommendations, assessment, development, and evaluation). The following recommendations were made:

- "We recommend the use of GH to normalize adult height and avoid extreme shortness in children and adolescents with GHD. (strong recommendation, high-quality evidence)"
- "We suggest a shared decision-making approach to pursuing GH treatment for a child with idiopathic short stature. The decision can be made on a case by case basis after assessment of physical and psychological burdens, and discussion of risks and benefits. We recommend against the routine use of GH in every child with height SDS [standard deviation score] ≤ -2.25. (conditional recommendation, moderate-quality evidence)"

In 2017, the PES published practice guidelines on the management of Turner syndrome based on proceedings of the International Turner Syndrome Meeting.[119,] The PES recommended initiating GH treatment early, around 4 to 6 years of age, and preferably before 12 to 13 years if the child had evidence of growth failure (<50th percentile height velocity) or had a strong likelihood of short stature (moderate quality of evidence).

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.[120,] 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.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Currently, ongoing or unpublished trials that might influence this review are listed in Table 9.

Table 9. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05330325[a]	A Study Comparing the Effect and Safety of Once Weekly Dosing of Somapacitan With Daily Norditropin® as Well as Evaluating Long-term Safety of Somapacitan in a Basket Study Design in Children With Short Stature Either Born Small for Gestational Age or With Turner Syndrome, Noonan Syndrome, or Idiopathic Short Stature	399	Sept 2026

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NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT05171855[a]	A Multicenter, Open-Label, Extension Trial to Investigate Long Term Efficacy and Safety of Lonapegsomatropin in Adults With Growth Hormone Deficiency	240	Jan 2025
NCT01604395[a]	An Open, Multi-Center, Prospective and Retrospective Observational Study to Evaluate the Long-term Safety and Effectiveness of Growth Hormone (Eutropin Inj./Eutropin plus Inj.) Treatment with GHD, TS, CRF, SGA, ISS, and PWS in Children	6000	Dec 2032
NCT04484051	Global Growth Hormone Study in Adults with Prader-Willi Syndrome	50	Oct 2026
NCT04615273[a]	foresiGHt: A Multicenter, Randomized, Parallel-arm, Placebo-controlled (Double-Blind) and Active-controlled (Open-label) Trial to Compare the Efficacy and Safety of Once-weekly Lonapegsomatropin With Placebo and a Daily Somatropin Product in Adults with Growth Hormone Deficiency	240	Dec 2024
Unpublished			
NCT00537914[a]	Long-term Phase IV Multicenter Study on the Safety and Efficacy of Omnitrope® (rhGH) in Short Children Born Small for Gestational Age (SGA)	278	Mar 2022 (completed)
NCT03038594	Growth Hormone Therapy for Muscle Regeneration in Severely Burned Patients	64	Nov 2021 (completed)
NCT01196156[a]	An Observational Phase IV Study for Prospective Follow-Up to Adult Height of a Cohort of Subjects Born Small for Gestational Age and Treated with Growth Hormone	443	Dec 2018 (completed)

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

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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
J2940	Injection, somatrem, 1 mg
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

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	Growth hormone has been approved for reimbursement subject to meeting all of the following criteria: a. Failure to respond (GH less than 15 ng/ml) to two hormones secretagogues (arginine, clonidine, glucagon, insulin, or levodopa) b. Height less than the 2.5 percentile c. Growth failure as defined by the following age groups: • 0 – 6 months: <34 cm/year • 6 – 12 months: <15 cm/year • 1 - 3 years: <12 cm/year • Over three years to puberty (see definition of puberty below): < 5 cm/year • Puberty (defined as bone age of 10 1/2 -12 years for girls and bone age of 12 1/2 -14 1/2 years for boys): <6 cm/year Note: Growth rates should be tracked over at least one year. Note: Continuation of treatment with growth hormone therapy requires a growth rate above 2.5 cm/year. 3. Panhypopituitarism Growth hormone has been approved for reimbursement subject to meeting all of the following criteria: a. Deficiencies of 2 or more other pituitary hormones (TSH, ACTH, FSH/LH, antidiuretic hormone) b. Low values for IGF-1 Note: Growth hormone stimulation testing is not required in these cases. Note: Growth hormone therapy may be approved for life. 4. Turner, Prader-Willi, and Noonan Syndromes With Growth Failure Growth hormone has been approved for reimbursement subject to meeting all of the following criteria: a. Height less than the 2.5 percentile for age and sex b. Growth failure as defined by the following age groups: • 0 – 6 months: < 34 cm/year • 6 – 12 months: < 15 cm/year • 1 - 3 years: <12 cm/year • Over three years to puberty (see below definition of puberty): <5 cm/year • Puberty (defined as bone age of 10 1/2-12 years for girls and bone age of 12 1/2 -14 1/2 years for boys): <6 cm/year Note: Growth rates should be tracked over at least one year. Note: Growth hormone stimulation testing is not required in these cases. 5. Managing Ongoing Renal Dialysis Patients With Growth Failure Growth hormone has been approved for reimbursement subject to meeting all of the following criteria: a. End stage renal disease with GFR less than 75 ml/min/1.73m2 prior to successful transplant b. Under age 18 c. With open epiphyses d. Height less than the 2.5 percentile for age and sex e. Growth failure as defined by the following age groups: • 0 – 6 months: <34 cm/year • 6 – 12 months: < 15 cm/year • 1 – 3 years: <12 cm/year • Over three years to puberty (see below definition of puberty): <5 cm/year

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	• Puberty (defined as bone age of 10 1/2-12 years for girls and bone age of 12 1/2 -14 1/2 years for boys): <6 cm/year f. Complicating factors have been treated including malnutrition and acidosis Note: Growth rates should be tracked over at least one year. Note: Growth Hormone stimulation testing is not required. <u>Termination of Growth Hormone Therapy</u> 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: <u>DOCUMENTATION</u> • 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

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	with documented multiple hormone deficiencies (3 or more deficiencies: secondary hypothyroidism, ACTH deficiency, gonadotropin deficiency, diabetes insipidus) as a result of pituitary or hypothalamic disease secondary to tumor, surgery, inflammation, radiation therapy, severe head trauma or structural abnormality (septo-optic dysplasia, ectopic neurohypophysis). Growth hormone stimulation testing is not necessary in these cases. 3. Continuation of approval for growth hormone therapy requires some indication of a clinical response to the growth hormone during the first 12 months of therapy; weight loss, improvement on lipid profile, increased bone mass, increased muscle strength or increase of IGF1 into the normal range. Children on growth hormone therapy who continue growth hormone therapy into adulthood or adults with hypopituitarism of recent onset will not exhibit the sequelae of adult growth hormone deficiency and will not show the improvements listed above. NOTE: If consultant decides that growth hormone treatment will be given for the rest of the life of the patient, it will no longer be necessary for Medical Review to re-review for medical necessity. It will be necessary, however, to review for benefits. <u>UTILIZATION</u> 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)."

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	▪ Added Item B 6, "Short bowel syndrome receiving specialized nutritional support in conjunction with optimal management of short bowel syndrome (see Policy Guidelines.)" ▪ In Policy Guidelines Item 3, added "Sleep studies are recommended prior to initiation of growth hormone therapy for obese pediatric patients with Prader-Willi syndrome." ▪ Added Policy Guidelines Items 5, 6, and 7. ▪ Added Policy Guidelines Item 8 e, "Neonatal hypoglycemia related to growth hormone deficiency." ▪ In Policy Guidelines Item 8, added "Children, Adolescents and Adults: a. AIDS wasting syndrome b. Short Bowel syndrome c. Severe burn patients"
	Updated Rationale section.
	In Coding section: ▪ 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:

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	▪ Added coding bullets. ▪ ICD-9 codes removed.
	Updated References section.
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

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	▪ In the Target Drugs Box added: "Omnitrope®" to the Preferred Growth Hormone list and removed it from the Nonpreferred list.
	Update Rationale Section
	Updated References Section

REFERENCES

1. 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
2. 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
3. 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
4. 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
5. 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
6. 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
7. 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
8. 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
9. 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
10. 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
11. 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

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Contains Public Information

12. Pfizer. Highlights of Prescribing Information: Genotropin (somatropin [rDNA origin] for injection). 2019; http://labeling.pfizer.com/ShowLabeling.aspx?id=577. Accessed August 21, 2023.
13. Eli Lilly. Highlights of Prescribing Information: Humatrope (somatropin [rDNA ORIGIN] for injection, for Subcutaneous Use). 2019; http://pi.lilly.com/us/humatrope-pi.pdf. Accessed August 21, 2023.
14. 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
15. 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
16. 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
17. 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
18. 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
19. 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
20. 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
21. 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
22. 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
23. 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
24. 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
25. 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
26. 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

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deficiency. A randomized, controlled clinical trial. Ann Intern Med. Jul 18 2000; 133(2): 111-22. PMID 10896637
27. 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
28. 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
29. 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
30. 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
31. 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
32. 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
33. 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
34. Craig ME, Cowell CT, Larsson P, et al. Growth hormone treatment and adverse events in Prader-Willi syndrome: data from KIGS (the Pfizer International Growth Database). Clin Endocrinol (Oxf). Aug 2006; 65(2): 178-85. PMID 16886957
35. Van Vliet G, Deal CL, Crock PA, et al. Sudden death in growth hormone-treated children with Prader-Willi syndrome. J Pediatr. Jan 2004; 144(1): 129-31. PMID 14722532
36. Grugni G, Livieri C, Corrias A, et al. Death during GH therapy in children with Prader-Willi syndrome: description of two new cases. J Endocrinol Invest. Jun 2005; 28(6): 554-7. PMID 16117198
37. 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
38. 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
39. 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
40. 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
41. 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

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Contains Public Information

42. 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
43. 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
44. 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
45. 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
46. 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
47. 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
48. 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
49. 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
50. 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
51. 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
52. 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
53. 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
54. 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
55. 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
56. 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
57. 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

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58. 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
59. 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
60. 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
61. 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
62. 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
63. 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
64. 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
65. 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
66. 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
67. 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
68. 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
69. 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
70. Idiopathic short stature: results of a one-year controlled study of human growth hormone treatment. Genentech Collaborative Study Group. J Pediatr. Nov 1989; 115(5 Pt 1): 713-9. PMID 2681637
71. Ackland FM, Jones J, Buckler JM, et al. Growth hormone treatment in non-growth hormone-deficient children: effects of stopping treatment. Acta Paediatr Scand Suppl. 1990; 366: 32-7. PMID 2206005
72. Cowell CT. Effects of growth hormone in short, slowly growing children without growth hormone deficiency. Australasian Paediatric Endocrine Group. Acta Paediatr Scand Suppl. 1990; 366: 29-30; discussion 31. PMID 2206004

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Contains Public Information

73. Leschek EW, Rose SR, Yanovski JA, et al. Effect of growth hormone treatment on adult height in peripubertal children with idiopathic short stature: a randomized, double-blind, placebo-controlled trial. J Clin Endocrinol Metab. Jul 2004; 89(7): 3140-8. PMID 15240584
74. McCaughey ES, Mulligan J, Voss LD, et al. Growth and metabolic consequences of growth hormone treatment in prepubertal short normal children. Arch Dis Child. Sep 1994; 71(3): 201-6. PMID 7979491
75. Barton JS, Gardineri HM, Cullen S, et al. The growth and cardiovascular effects of high dose growth hormone therapy in idiopathic short stature. Clin Endocrinol (Oxf). Jun 1995; 42(6): 619-26. PMID 7634503
76. Soliman AT, abdul Khadir MM. Growth parameters and predictors of growth in short children with and without growth hormone (GH) deficiency treated with human GH: a randomized controlled study. J Trop Pediatr. Oct 1996; 42(5): 281-6. PMID 8936959
77. Kamp GA, Waelkens JJ, de Muinck Keizer-Schrama SM, et al. High dose growth hormone treatment induces acceleration of skeletal maturation and an earlier onset of puberty in children with idiopathic short stature. Arch Dis Child. Sep 2002; 87(3): 215-20. PMID 12193430
78. Volta C, Bernasconi S, Tondi P, et al. Combined treatment with growth hormone and luteinizing hormone releasing hormone-analogue (LHRHa) of pubertal children with familial short stature. J Endocrinol Invest. Nov 1993; 16(10): 763-7. PMID 8144848
79. McCaughey ES, Mulligan J, Voss LD, et al. Randomised trial of growth hormone in short normal girls. Lancet. Mar 28 1998; 351(9107): 940-4. PMID 9734940
80. Albertsson-Wikland K, Aronson AS, Gustafsson J, et al. Dose-dependent effect of growth hormone on final height in children with short stature without growth hormone deficiency. J Clin Endocrinol Metab. Nov 2008; 93(11): 4342-50. PMID 18728172
81. Hindmarsh PC, Brook CG. Effect of growth hormone on short normal children. Br Med J (Clin Res Ed). Sep 05 1987; 295(6598): 573-7. PMID 3117236
82. Wit JM, Rietveld DH, Drop SL, et al. A controlled trial of methionyl growth hormone therapy in prepubertal children with short stature, subnormal growth rate and normal growth hormone response to secretagogues. Dutch Growth Hormone Working Group. Acta Paediatr Scand. May 1989; 78(3): 426-35. PMID 2662700
83. Volta C, Ghizzoni L, Muto G, et al. Effectiveness of growth-promoting therapies. Comparison among growth hormone, clonidine, and levodopa. Am J Dis Child. Feb 1991; 145(2): 168-71. PMID 1994682
84. Lanes R. Effects of two years of growth hormone treatment in short, slowly growing non-growth hormone deficient children. J Pediatr Endocrinol Metab. 1995; 8(3): 167-71. PMID 8521190
85. Tao S, Li G, Wang Q, et al. Efficacy and Safety of Human Growth Hormone in Idiopathic Short Stature. Indian J Pediatr. Jul 2015; 82(7): 625-8. PMID 25893526
86. Zadik Z, Mira U, Landau H. Final height after growth hormone therapy in peripubertal boys with a subnormal integrated concentration of growth hormone. Horm Res. 1992; 37(4-5): 150-5. PMID 1490656
87. Wit JM, Boersma B, de Muinck Keizer-Schrama SM, et al. Long-term results of growth hormone therapy in children with short stature, subnormal growth rate and normal growth hormone response to secretagogues. Dutch Growth Hormone Working Group. Clin Endocrinol (Oxf). Apr 1995; 42(4): 365-72. PMID 7750190
88. Hindmarsh PC, Brook CG. Final height of short normal children treated with growth hormone. Lancet. Jul 06 1996; 348(9019): 13-6. PMID 8691923

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Contains Public Information

89. Buchlis JG, Irizarry L, Crotzer BC, et al. Comparison of final heights of growth hormone-treated vs. untreated children with idiopathic growth failure. J Clin Endocrinol Metab. Apr 1998; 83(4): 1075-9. PMID 9543120
90. López-Siguero JP, García-Garcia E, Carralero I, et al. Adult height in children with idiopathic short stature treated with growth hormone. J Pediatr Endocrinol Metab. 2000; 13(9): 1595-602. PMID 11154155
91. Coutant R, Rouleau S, Despert F, et al. Growth and adult height in GH-treated children with nonacquired GH deficiency and idiopathic short stature: the influence of pituitary magnetic resonance imaging findings. J Clin Endocrinol Metab. Oct 2001; 86(10): 4649-54. PMID 11600520
92. Wit JM, Rekers-Mombarg LT. Final height gain by GH therapy in children with idiopathic short stature is dose dependent. J Clin Endocrinol Metab. Feb 2002; 87(2): 604-11. PMID 11836292
93. van Gool SA, Kamp GA, Odink RJ, et al. High-dose GH treatment limited to the prepubertal period in young children with idiopathic short stature does not increase adult height. Eur J Endocrinol. Apr 2010; 162(4): 653-60. PMID 20110402
94. Lopez-Siguero JP, Martinez-Aedo MJ, Moreno-Molina JA. Final height after growth hormone therapy in children with idiopathic short stature and a subnormal growth rate. Acta Pediatr. 1996;85:113-57.
95. 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
96. 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
97. 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
98. 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
99. 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
100. 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
101. 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
102. 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
103. 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

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Contains Public Information

104. 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
105. 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
106. 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
107. 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
108. Yuen KCJ, Biller BMK, Radovick S, et al. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF GROWTH HORMONE DEFICIENCY IN ADULTS AND PATIENTS TRANSITIONING FROM PEDIATRIC TO ADULT CARE. Endocr Pract. Nov 2019; 25(11): 1191-1232. PMID 31760824
109. Iyer K, DiBaise JK, Rubio-Tapia A. AGA Clinical Practice Update on Management of Short Bowel Syndrome: Expert Review. Clin Gastroenterol Hepatol. Oct 2022; 20(10): 2185-2194.e2. PMID 35700884
110. Fleseriu M, Hashim IA, Karavitaki N, et al. Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. Nov 2016; 101(11): 3888-3921. PMID 27736313
111. Sklar CA, Antal Z, Chemaitilly W, et al. Hypothalamic-Pituitary and Growth Disorders in Survivors of Childhood Cancer: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. Aug 01 2018; 103(8): 2761-2784. PMID 29982476
112. Cohen P, Rogol AD, Deal CL, et al. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. J Clin Endocrinol Metab. Nov 2008; 93(11): 4210-7. PMID 18782877
113. Deal CL, Tony M, Höybye C, et al. GrowthHormone Research Society workshop summary: consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. J Clin Endocrinol Metab. Jun 2013; 98(6): E1072-87. PMID 23543664
114. Allen DB, Backeljauw P, Bidlingmaier M, et al. GH safety workshop position paper: a critical appraisal of recombinant human GH therapy in children and adults. Eur J Endocrinol. Feb 2016; 174(2): P1-9. PMID 26563978
115. Collett-Solberg PF, Ambler G, Backeljauw PF, et al. Diagnosis, Genetics, and Therapy of Short Stature in Children: A Growth Hormone Research Society International Perspective. Horm Res Paediatr. 2019; 92(1): 1-14. PMID 31514194
116. 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
117. 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

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Blue Cross and Blue Shield Kansas is an independent licensee of the Blue Cross Blue Shield Association

Contains Public Information

118. Grimberg A, DiVall SA, Polychronakos C, et al. Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency. Horm Res Paediatr. 2016; 86(6): 361-397. PMID 27884013
119. Gravholt CH, Andersen NH, Conway GS, et al. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol. Sep 2017; 177(3): G1-G70. PMID 28705803
120. National Institute for Health and Care Excellence (NICE). Human growth hormone (somatropin) for growth failure in children [TA188]. 2013; https://www.nice.org.uk/guidance/ta188. Accessed August 21, 2023.

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.

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