Policy Number	RX501.040
Policy Effective Date	01/01/2026

Human Growth Hormone (GH)

Table of Contents
Coverage
Policy Guidelines
Description
Rationale
Coding
References
Policy History

Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

EXCEPTION: For members residing in the state of Maine, 24-A s 2837-G and 24-A s 4234-E (for HMOs) requires all group insurance policies and all health maintenance organization group contracts that provide coverage for prescription drugs must provide coverage for off-label use in accordance with the following: A) Group policies that provide coverage for prescription drugs may not exclude coverage of any such drug used for the treatment of HIV or AIDS on the grounds that the drug has not been approved by the federal Food and Drug Administration for that indication, as long as that drug is recognized for the treatment of that indication in one of the standard reference compendia or in peer-reviewed medical literature. B) Coverage of a drug required by this subsection also includes medically necessary services associated with the administration of the drug. C) This subsection may not be construed to require coverage for a drug when the federal Food and Drug Administration has determined its use to be contraindicated for treatment of the current indication. D) A drug use that is covered pursuant to paragraph A may not be denied coverage based on a "medical necessity" requirement except for a reason that is unrelated to the legal status of the drug use. E) A contract that provides coverage of a drug as required by this subsection may contain provisions for maximum benefits and coinsurance and reasonable limitations, deductibles and exclusions to the same extent that these provisions are applicable to coverage of all prescription drugs and are not inconsistent with the requirements of this subsection. For this provision: “Off-label use" means the prescription and use of drugs for indications other than those stated in the labeling approved by the federal Food and Drug Administration. "Peer-reviewed medical literature" means scientific studies published in at least 2 articles from major peer-reviewed medical journals that present data that supports the proposed off-label use as generally safe and effective. "Standard reference compendia" means: a. The United States Pharmacopeia Drug Information or information published by its successor organization; or b. The American Hospital Formulary Service Drug Information or information published by its successor organization. This applies to Fully Insured Small Group, Mid-Market, Large Group, Student PPO, HMO, POS, EPO.

EXCEPTION: For members residing in the state of Maine, 24-A s 2837-F and 24-A s 4234-D (for HMOs) requires that coverage for prescription drugs must provide coverage for off-label use in accordance with the following: A) Group insurance policies that provide coverage for prescription drugs may not exclude coverage of any such drug used for the treatment of cancer for a medically accepted indication on the grounds that the drug has not been approved by the federal Food and Drug Administration for that indication, as long as that use of that drug is a medically accepted indication for the treatment of cancer. B) Coverage of a drug required by this subsection also includes medically necessary services associated with the administration of the drug. C) This subsection may not be construed to require coverage for a drug when the federal Food and Drug Administration has determined its use to be contraindicated for treatment of the current indication. D) A drug use that is covered pursuant to paragraph A may not be denied coverage based on a "medical necessity" requirement except for a reason that is unrelated to the legal status of the drug use. E) A contract that provides coverage of a drug as required by this subsection may contain provisions for maximum benefits and coinsurance and reasonable limitations, deductibles and exclusions to the same extent that these provisions are applicable to coverage of all prescription drugs and are not inconsistent with the requirements of this subsection. For this requirement: "Medically accepted indication" includes any use of a drug that has been approved by the federal Food

and Drug Administration and includes another use of the drug if that use is supported by one or more citations in the standard reference compendia or if the insurer involved, based upon guidance provided by the federal Department of Health and Human Services Medicare program pursuant to 42 United States Code, Section 1395x(t), determines that that use is medically accepted based on supportive clinical evidence in peer-reviewed medical literature. "Off-label use" means the prescription and use of drugs for medically accepted indications other than those stated in the labeling approved by the federal Food and Drug Administration. "Peer-reviewed medical literature" means scientific studies published in at least 2 articles from major peer-reviewed medical journals that present data that supports the proposed off-label use as generally safe and effective. "Standard reference compendia" means: a). The United States Pharmacopeia Drug Information or information published by its successor organization; or b). The American Hospital Formulary Service Drug Information or information published by its successor organization. This applies to Fully Insured Small Group, Mid-Market, Large Group, Student PPO, HMO, POS, EPO.

EXCEPTION: For members residing in the state of Nebraska, §44-788 (Drug Coverage for the Treatment of Cancer and AIDS) mandates that any individual or group policy which provides reimbursement for FDA approved prescription drugs for the treatment of a specific type of cancer OR human immunodeficiency virus or acquired immunodeficiency syndrome shall not exclude coverage of any drug or combination of drugs on the basis that the drug or combination of drugs has not been approved by the federal Food and Drug Administration for the treatment of another specific type of cancer OR human immunodeficiency virus or acquired immunodeficiency syndrome if: (a) the drug or combination of drugs is recognized for treatment of the other specific type of cancer OR human immunodeficiency virus or acquired immunodeficiency syndrome in the United States Pharmacopeia-Drug Information and the drug or combination of drugs is approved for sale by the federal Food and Drug Administration, or (b) the drug or combination of drugs is recognized for treatment of the other specific type of cancer OR human immunodeficiency virus or acquired immunodeficiency syndrome in medical literature and the drug or combination of drugs is approved for sale by the federal Food and Drug Administration. For purposes of this section, medical literature means two articles from major peer-reviewed professional medical journals that have recognized, based on scientific or medical criteria, the safety and effectiveness of the drug or combination of drugs for treatment of the indication for which it has been prescribed unless two articles from major peer-reviewed professional medical journals have concluded, based on scientific or medical criteria, that the drug or combination of drugs is unsafe or ineffective or that the safety and effectiveness of the drug or combination of drugs cannot be determined for the treatment of the indication for which the drug or combination of drugs has been prescribed. Each article shall meet the uniform requirements for manuscripts submitted to biomedical journals established by the International Committee of Medical Journal Editors or shall have been published in a journal specified by the United States Department of Health and Human Services pursuant to 42 U.S.C. 1395x(t)(2)(B), as amended, as acceptable peer-reviewed medical literature. Peer-reviewed medical literature shall not include publications or supplements that are sponsored to a significant extent by a pharmaceutical manufacturing company or health carrier.
Further, the coverage of a drug or combination of drug under this section shall include medically necessary services associated with the administration of the drug if such services are covered by the policy. This applies to: Fully Insured Small Group, Mid-Market, Large Group, Student PPO, HMO, POS, EPO. Unless indicated by the group, this mandate or coverage will not apply to ASO groups.

Coverage

ALERT 1: The Description section of this policy contains a list of growth hormone (GH) products and/or indications which is not all-inclusive. Please verify current labeling at FDA <https://access.data.gov>

ALERT 2: All self-injectable medications are administered under the pharmacy benefit.

Food and Drug Administration Labeled Indications For Human Growth Hormone

Growth hormone (GH) therapy **may be considered medically necessary** for the following Food and Drug Administration (FDA) approved indications (see Table 1A/1B):

1. Growth failure/growth deficiency in pediatric patients with inadequate endogenous growth hormone (GH) or GH deficiency:
   - Failed **TWO** provocative GH stimulation tests, each with peak value < 10 ng/ml. (e.g. growth hormone releasing hormone (GHRH), arginine, insulin, L-dopa, clonidine, or glucagon); **OR**
   - Documentation of height at least 2.0 standard deviations (SD) below mean over one year or more OR more than 1.5 SDs sustained over two years, AND **Documentation** of GHD resulting from either:
     a) A destructive lesion of the pituitary;
     b) A medical treatment, including but not limited to ablative pituitary radiation or surgery;
     c) Central nervous system pathology;
     d) Genetic Defect (Turner syndrome, Noonan syndrome, Prader-Willi syndrome, SHOX **deficiency**) NOTE: For patients with Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment, growth hormone is contraindicated due to the risk of sudden death; or
     e) Trauma.
2. Replacement therapy/GH deficiency (GHD) in adults with growth hormone deficiency
   - Failed TWO provocative GH stimulation tests (e.g., insulin AND one of the growth hormone-releasing hormone preparations as an adult; **OR**
   - Failed ONE provocative GH stimulation tests (e.g., insulin or one of the growth hormone-releasing hormone preparations as an adult (see Policy Guidelines); AND documentation of GHD resulting from:
     a) A destructive lesion of the pituitary; or
     b) A medical treatment, including but not limited to ablative pituitary radiation or surgery; or
     c) Central nervous system pathology; or
     d) Genetic defect (Noonan syndrome, Prader Willi syndrome, SHOX deficiency, Turner Syndrome); or
     e) Low concentration of insulin-like growth factor-1 (IGF-1) with complete hypopituitarism; or
     f) Trauma.
3. Idiopathic short stature, when epiphysis is not closed, defined by height SDS ≤-2.25 in non-GHD pediatric patients when height is less than 3rd percentile for chronological age.

4. Chronic renal insufficiency associated with growth failure.
5. Human immunodeficiency virus (HIV) wasting or cachexia.
6. Treatment of short bowel syndrome.
7. Children born small for gestational age, who fail to show catch-up growth by age 2 years.

Off-Label Use Of Human Growth Hormone

Off-label use of recombinant human growth hormone (GH) therapy **may be considered medically necessary** for:

1. The promotion of wound healing in individuals with 3rd degree burns.
2. The prevention of growth delay in children with 3rd degree burns when:
    - The burns have been successfully treated with recombinant Growth Hormone 0.05 to 0.2 mg/kg/d during acute hospitalization; and
    - For up to 1 year after a burn.

Recombinant human growth hormone **is considered experimental, investigational, and/or unproven** for all other off-label applications including, but not limited to the following:

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

Contraindications To The Use Of Growth Hormone (FDA Labeled And Off Label)

Growth hormone is contraindicated in the following situations:

- Acute critical illness after open heart surgery, abdominal surgery or multiple accidental trauma or those with acute respiratory failure due to the risk of increased mortality with use of pharmacologic doses of somatropin.

- Active malignancy.
- Active proliferative or severe non-proliferative diabetic retinopathy.
- Pediatric patients with closed epiphyses.

Policy Guidelines

- The FDA defines Idiopathic Short Stature (ISS) is a height standard deviation score (SDS) <-2.25 and associated with growth rates unlikely to permit attainment of adult height in the normal range. (1)
- Insulin Provocation is the gold standard for confirming GHD in most adults. It must be ONE of the TWO tests provided for documentation of GHD unless the test is contraindicated because the individual has history of seizures, is elderly, or has coronary artery disease/cerebrovascular disease. (82)
- When a diagnosis of GHD is established for an adult, and therapy with GH is initiated, **documentation** may be requested at 1- to 2-year intervals to demonstrate that the individual is obtaining measurable clinical benefit from GH therapy. A physician should consider a trial of withdrawal of GH therapy for individuals who do not have demonstrated clinical benefit. (82)
- In children, growth Hormone (GH) therapy is typically discontinued when the growth velocity is below 2.0 to 2.5 cm/year; when epiphyseal fusion has occurred; or when the height reaches the 5th percentile of adult height. (1, 80)
- Diagnostic guidelines for an abnormal GH response in stimulation tests are highly dependent on the assay type, stimulating agent, patient's body mass index (BMI), age, and clinical context. Because of these factors, the traditional cutoff of less than 10 ng/mL is no longer considered universal. The use of more sensitive monoclonal antibody-based assays and modern recombinant human GH (rhGH) reference preparations has led to lower peak GH cutoffs than those used with older, less specific polyclonal radioimmunoassays. (91)
- In children with documented GHD, once adult height has been achieved, individuals should be re-tested as adults to determine if continuing GH replacement therapy is medically appropriate. (84)

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).

Growth Hormone

Human GH, also known as somatotropin, is synthesized in somatotropic cells of the anterior lobe of the pituitary gland. GHD can occur due to 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 (GHD) in children is manifested primarily by short stature. In adults, as well as in some children, other abnormalities associated with GHD are often evident. They include changes in body composition, higher levels of low-density lipoprotein cholesterol, lower bone density, and a decreased self-reported quality of life compared with healthy peers. Some evidence has suggested that there may be increases in cardiovascular disease and overall mortality, but it is less clear whether GHD causes these outcomes.

Outcome Measures in GH Research

The most common outcome measure reported in GH research is change in height. For some situations, such as in patients with documented GHD or genetic disorder and short stature, improvements in height alone may be a sufficient outcome measure. However, in most situations, a change in height is not in itself sufficient to demonstrate that health outcomes are improved. There is insufficient evidence to establish that short stature is associated with substantial impairments in psychological functioning or QOL, 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 policy, changes in other outcome measures, (e.g., functional status, QOL, 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 1A and 1B). (1) Table 2 provides a summary of recognized on-label uses and supporting references. (2-50)

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

Indications	Genotropin® (Pfizer)	Humatrope® (Lilly)	Norditropin ® (Novo-Nordisk)	Nutropin® (Genentech)	Saizen® (Serono)	Serostim® (Serono)
Growth failure, pediatric patients with inadequate endogenous GH	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	
Replacement therapy in adults with GHD	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	

Growth failure due to Prader-Willi syndrome	**Yes**		**Yes**			
Growth failure associated with chronic renal insufficiency				**Yes**		
Short stature due to Turner syndrome (45,XO)	**Yes**	**Yes**	**Yes**	**Yes**		
Short stature in pediatrics patients with Noonan syndrome			**Yes**			
Short stature in pediatrics patients with SHOX deficiency		**Yes**				
HIV wasting or cachexia						**Yes**
Treatment of short bowel syndrome						
Children born small for gestational age, who fail to show catch-up growth by age 2 y	**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; HIV: human immunodeficiency virus; SDS: standard deviation score; SHOX: short stature homeobox-containing gene; y: year.

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

Indications	Zomacton®[a] (Ferring)	Zorbtive® (Serono)	Omnitrope® (Sandoz)	Sogroya® (Novo-Nordisk)	Skytrofa® (Ascendis Pharma)	Ngenla® (Pfizer)
Growth failure, pediatric patients with inadequate endogenous GH	**Yes**		**Yes**	**Yes**	**Yes**	**Yes**
Replacement therapy in adults with GHD	**Yes**		**Yes**	**Yes**		
Growth failure due to Prader-Willi syndrome			**Yes**			
Growth failure associated with chronic renal insufficiency						
Short stature due to Turner syndrome (45,XO)	**Yes**		**Yes**			
Short stature in pediatrics patients with Noonan syndrome						
Short stature in pediatrics patients with SHOX deficiency	**Yes**					
HIV wasting or cachexia,						
Treatment of short bowel syndrome		**Yes**				
Children born small for gestational	**Yes**		**Yes**			

age, who fail to show catch-up growth by age 2 y						
Idiopathic short stature, defined by height SDS ≤-2.25 in non-GHD pediatric patients	**Yes**		**Yes**			

GH: growth hormone; GHD: growth hormone deficiency; HIV: human immunodeficiency virus; SDS: standard deviation score; SHOX: short stature homeobox-containing gene; y: year.

Table 2. U.S. FDA Approved Indications and Supporting References

Indications	**Supporting References**
Proven GH deficiency	<u>GHD in children:</u> Root et al. 1998 (2) Reiter et al. 2006 (3) Thornton et al. 2021 (4) Maniatis et al. 2022 (5) Savendahl et al. 2022 (6) <u>GHD in adults:</u> Beauregard et al. 2008 (7) Widdowson et al. 2008 (8) Widdowson et al. 2010 (9) Xue et al. 2013 (10) Barake et al. 2014 (11) Hoffman et al. 2004 (12) Maison et al. 2003 (13) Sesmilo et al. 2000 (14) Gotherstrom et al. 2001 (15) Dutta et al. 2022 (16) Ishii et al. 2017 (17)
Short stature due to Prader Willi syndrome	Frixou et al. 2021 (18) Luo et al. 2021 (19) Passone et al. 2020 (20) Kuppens et al. 2016 (21)
Short stature due to chronic renal insufficiency	Wu et al. 2013 (22) Hodson et al. 2012 (23) Hokken-Koelega et al .1991 (24) Hokken-Koelega et al. 2000 (25)

Short stature due to Turner syndrome	Li et al. 2018 (26) Baxter et al. 2007 (27) Juloski et al. 2016 (28)
Short stature due to Noonan syndrome	Giacomozzi et al. 2015 (29) MacFarlane et al. 2001 (30)
Short stature due to SHOX	Takeda et al. 2010 (31) Blum et al. 2007 (32) Benabbad et al. 2017 (33) Child et al. 2019 (34) Bruzzi et al. 2023 (35)
HIV/AIDS wasting or cachexia	Moyle et al. 2004 (36) Evans et al. 2005 (37)
Short bowel syndrome on specialized nutritional support	Wales et al. 2010 (38) Scolapio 1999 (39) Seguy et al. 2003 (40) Szkudlarek et al. 2000 (41)
Individuals who are small for gestational age in childhood	Maiorana and Cianfarani 2009 (42) Juul et al. 2023 (43)
Idiopathic short stature	Bryant et al. 2007 (44) Deodati and Cianfarani 2011 (45) Paltoglou et al. 2020 (46) Shemesh-Iron et al. 2019 (47) Ross et al. 2004 (48) Theunissen et al. 2002 (49) Downie et al. 1996 (50)

FDA: Food and Drug Administration; GH: growth hormone; GHD: growth hormone deficiency; SHOX; short stature homeobox-containing gene; U.S.: United States.

Rationale

FOOD AND DRUG ADMINISTRATION (FDA) APPROVED INDICATIONS FOR GROWTH HORMONE

For FDA approved indications, this policy is supported by the individual product labels (1), clinical studies within those labels and society guidelines. (77-90)

Per the FDA, Growth Hormone (GH) is contraindicated in the following situations (1):

- Acute critical illness after open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure due to the risk of increased mortality with use of pharmacologic doses of somatropin.
- Pediatric patients with Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment due to the risk of sudden death.
- Active malignancy.

- Known hypersensitivity to somatropin or any of the excipients. Systemic hypersensitivity
- reactions have been reported with postmarketing use of somatropins.
- Active proliferative or severe non-proliferative diabetic retinopathy.
- Pediatric patients with closed epiphyses (growth plate).

In children, GH therapy is typically discontinued when the growth velocity is below 2.0 to 2.5 cm/year; when epiphyseal fusion (growth plate) has occurred; or when the height reaches the 5th percentile of adult height. (1, 80)

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use 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. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Safety of Growth Hormone Treatment
Adverse events can occur with 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. (51-53) 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. (54) 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. (55) PATRO Adult included 1293 patients as of July 2018 from 76 sites in 8 European countries; enrollees who received ≥1 dose of Omnitrope were included in the safety population. Of these patients, 33 developed on-study malignancies (2.6%; incidence rate of 7.94 per 1000 patient-years) with tumors occurring after a mean of 79.4 months of GH treatment overall. Seven patients experienced >1 malignancy occurrence (n=41 total malignancies). Of the 33 patients, 3 had no prior medical history of malignancies or tumors. The most commonly occurring malignancies included basal cell carcinoma (n=13), prostate (n=6), breast (n=3), kidney (n=3), and malignant melanoma (n=3) and the majority occurred in patients >50 years of age (35 out of 41 cases). GH treatment was discontinued following malignancy diagnosis in 15 patients. Backeljauw et al. (2022) published results of the analogous PATRO Children study. (56) 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). (57) 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 GH Treatments in Europe study, which compared the risk of cancer mortality and cancer incidence among patients receiving GH therapy with national population rates. (58) 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). (59) 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 (ISS) (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 6,558 (94.7%) of participants. Ninety-three (1.42%) of the 6,558 individuals had died. The mortality rate was significantly higher in patients treated with GH than would be expected on the basis of year, sex, or age (standardized mortality ratio, 1.33; 95% CI, 1.08 to 1.64). Examination of the causes of death found a significant increase in mortality due to circulatory system diseases. In addition, there was a significant increase in the number of deaths due to bone tumors (3 observed deaths vs 0.6 expected deaths) but no other types of cancers or overall cancer deaths. There was also a significant increase in the number of deaths due to cerebral or subarachnoid hemorrhage (4 observed deaths versus 0.6 expected).

Poidvin et al. (2014) reported on the same data, focusing on the risk of stroke in adulthood among childhood users of GH therapy. (60) This analysis included 6,874 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 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). (61) 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.

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 individuals with severe burns.

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

Populations

The relevant population of interest is individuals with severe burns.

Interventions

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

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

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. (62) 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). Reviewers also performed a meta-analysis of studies that did not conduct survival analyses but did follow

patients until their wounds healed. These analyses found significantly shorter healing time in patients who received GH therapy among adults (2 studies) and among children (2 studies). A pooled analysis of 5 studies did not find a statistically significant difference in mortality among patients receiving GH therapy and placebo (relative risk, 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 (relative risk=2.65; 95% CI, 1.68 to 4.16).

Randomized Controlled Trials

An RCT by Knox et al. (1995) measuring mortality included 54 adult burn patients who survived the first 7 postburn days. (63) Those patients showing difficulty with wound healing were treated with human GH and compared with those healing at the expected rate with standard therapy. Mortality of GH-treated patients was 11% compared with 37% for those not receiving GH (p=0.027). Infection rates were similar in both groups.

Singh et al. (1998) studied 2 groups of patients (n=22) with comparable third-degree burns; those who received GH had improved wound healing and a lower mortality rate (8% vs 44%). (64) 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. (65)

Prevention of Growth Delay in Children with Severe Burns

Children with severe burns show significant growth delays for up to 3 years after injury. GH treatment in 72 severely burned children for 1 year after discharge from intensive care resulted in significantly increased height in a placebo-controlled, randomized, double-blind trial. (66) 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 burn compared with a similar group of untreated children. (67)

Section Summary: Severe Burns

For individuals who have severe burns who receive human GH, the evidence includes RCTs and a meta-analysis. The meta-analysis found significantly shorter healing times and significantly shorter hospital stays with GH therapy than with placebo. Several RCTs have found significantly greater height gain in children with burns who received GH therapy versus placebo or no treatment.

Altered Body Habitus Related to Antiretroviral Therapy for Human Immunodeficiency Virus (HIV) 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 individuals with altered body habitus related to antiretroviral therapy for HIV infection.

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

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.

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 retroviral therapy. (68) Participants were randomized to GH 0.7 mg/day (n=24) or placebo (n=18) for 40 weeks. The primary outcome was change in inflammation measured by C-reactive protein and soluble urokinase plasminogen activator receptor, both of which increase with inflammation. After 40 weeks, low-dose GH significantly lowered C-reactive protein. Low-dose GH lowered soluble urokinase plasminogen activator receptor 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. (69) The authors reported improved waist/hip ratio and mid-thigh circumference.

Section Summary: Altered Body Habitus Related to Antiretroviral Therapy for HIV 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 a case series. The RCT measured the effect of low-dose GH on intermediate outcomes (inflammation markers). Case series data are insufficient for drawing conclusions about the impact of GH treatment on health outcomes in HIV infected patients with altered body habitus due to antiretroviral therapy. Controlled studies reporting relevant outcomes are needed.

Children With "Genetic Potential"

Clinical Context and Therapy Purpose

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

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

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.

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 high 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 individuals with precocious puberty.

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

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 two 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.

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. (70) 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 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, 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 the height outcomes were found.

Randomized Controlled Trials

One RCT compared GnRH analogs alone with GnRH analogs plus GH therapy. This trial, by Tuvemo et al. (1999), included 46 girls with precocious puberty. (71) Criteria for participation did not include predicted adult height or growth velocity. After 2 years of treatment, mean growth and predicted adult height was greater in those receiving combined treatment than in those receiving GnRH analogues 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 an RCT. While the meta-analysis included RCTs and controlled trials, only 1 RCT and 4 controlled trials provided data for the meta-analyses 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 GHD

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

The therapy being considered is human GH.

Comparators

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

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

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

A systematic review (2001) investigated the use of GH in older adults with age-related GHD and concluded tha there was insufficient evidence of efficacy It is not possible to prove the effectiveness of GH treatment or lack of 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 GHD
For individuals who are older adults with age-related GHD who receive human GH, the evidence includes a systematic review. There is a lack of evidence that GH therapy in older adults improves health outcomes. No subsequent controlled studies were identified.

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

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

Populations
The relevant population of interest is individuals with CF.

Interventions
The therapy being considered is human GH.

Comparators

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

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

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

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

An update to the Cochrane review by Thaker et al. was published in 2018. (73) Eight trials (291 participants) were included in the revision, of which 7 compared standard-dose recombinant human growth hormone (rhGH; approximately 0.3 mg/kg/week) to no treatment and 1,3-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 showed modest improvement in height, weight, and lean body mass between 6 and 12 months, but there was no consistent evidence that rhGH improved lung function, muscle strength, or QOL. A subsequent review in 2021 did not find any new studies to add, and the authors concluded that further randomized trial data is needed to justify routine clinical use. (74)

Previously, a systematic review by Phung et al. (2010) identified 10 controlled trials evaluating GH for treating patients with CF. (75) One study was placebo-controlled, 8 compared GH therapy with no treatment, and the remaining trial compared GH alone with glutamine or glutamine plus GH. Treatment durations ranged from 4 weeks to 1 year. There were insufficient data to determine the effect of GH on most health outcomes (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). (76) It compared GH therapy with no treatment in prepubertal children with CF younger than 14 years of age. Eligibility criteria included height <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 ($p<0.001$). The mean height SDS in the treatment group was -1.8 at baseline, -1.4 at 12 months, and -1.4 at 18 months vs -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 ($p<0.001$). Between months 12 and 18, the control group remained at the same height SDS, while the treatment group experienced a slight decline (0.1 SDS) but maintained a 0.5 SDS advantage over the control group.

In terms of pulmonary outcomes, the unadjusted rate of change from baseline to 12 months for most variables (7 of 8 pulmonary test results) did not differ between groups. However, the unadjusted change from 12 to 18 months (after treatment ended) was significantly greater in the control group than in the treatment group for 4 of 7 pulmonary test variables, including forced expiratory volume in 1 second ($p<0.005$) and forced vital capacity ($p<0.01$). In the treatment group, mean forced expiratory volume in 1 second was 1209 liters at baseline, 1434 liters at 12 months, and 1467 liters at 18 months compared with 1400 liters at baseline, 1542 liters at 12 months, and 1674 liters 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: CF

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 the 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.

Summary of Evidence

Food And Drug Administration (FDA) Approved Indications For Growth Hormone
For FDA approved indications for Growth Hormone, this policy is supported by the individual product labels, clinical studies within those labels and society guidelines.

For Off-Label Use
For individuals who have severe burns (3rd degree) who receive human growth hormone (GH) the evidence includes RCTs and a meta-analysis. Relevant outcomes are symptoms, hospitalizations, and treatment-related morbidity. The meta-analysis found significantly shorter healing times and significantly shorter hospital stays with GH therapy than with placebo. Several randomized controlled trials (RCTs) have found significantly greater height gain in children with burns who received GH therapy versus placebo or no treatment. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have altered body habitus related to antiretroviral therapy for human immunodeficiency virus (HIV) infection who receive human GH, the evidence includes a RCT and case series. Relevant outcomes are functional outcomes, quality of life (QOL), and treatment-related morbidity. 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 patients with HIV with altered body habitus due to antiretroviral therapy. Controlled studies reporting relevant outcomes are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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. Relevant outcomes are functional outcomes, QOL, and treatment-related morbidity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have precocious puberty who receive human GH plus gonadotropin-releasing hormone (GnRH), the evidence includes a meta-analysis and a RCT. Relevant outcomes are functional outcomes, QOL, and treatment-related morbidity. 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are older adults with age-related GH deficiency (GHD) who receive human GH, the evidence includes a systematic review. Relevant outcomes are functional outcomes, QOL, and treatment-related morbidity. The systematic review concluded there is a lack of evidence that GH therapy in older adults improves health outcomes. No subsequent controlled

studies were identified. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have cystic fibrosis (CF) who receive human GH, the evidence includes RCTs and systematic reviews. Relevant outcomes are functional outcomes, QOL, and treatment-related morbidity. 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American Academy of Pediatrics

In 2016, the American Academy of Pediatrics published guidelines on the evaluation and referral of children with signs of early puberty. (77) The use of GnRH analogues was discussed as treatment options, but GH as a treatment option was not discussed.

Pediatric Endocrine Society

In 2015, the Pediatric Endocrine Society (PES) published an evidence-based report focusing on the risk of neoplasia in patients receiving GH therapy. (78) The report concluded that GH therapy can be administered without concerns about the impact on neoplasia in children without known risk factors for malignancy. For children with medical conditions associated with an increased risk of future malignancies, patients should be evaluated on an individual basis and decisions made about the tradeoff between a possible benefit of GH therapy and possible risks of neoplasm.

As an addendum to the 2015 guidelines, Grimberg and Allen (2017), guideline coauthors, published a historical review of the use of GH. (79) They asserted that although the guidelines did not find an association between GH and neoplasia, the use of GH should not necessarily be expanded. While the use of GH for patients with GHD was recommended, evidence gaps persist in the use of GH for other indications such as ISS and partial isolated GHD.

In 2016, 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 were published. (80) The guidelines used the GRADE approach (grading of recommendations, assessment, development, and evaluation). The following recommendations were made:

- “1.1 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)"
- “2.1.1. We suggest establishing a diagnosis of GHD without GH provocative testing in patients possessing ALL the following conditions: auxological criteria, hypothalamic-pituitary

defect (such as major congenital malformation [ectopic posterior pituitary and pituitary hypoplasia with abnormal stalk], tumor or irradiation), and deficiency of at least one additional pituitary hormone. (Conditional recommendation)"

- "2.2.1 We recommend against reliance on GH provocative test results as the sole diagnostic criterion of GHD. (Strong recommendation) Given the substantial number of healthy, normally growing children who test below accepted limits, inadequate response to two different provocative tests is required for diagnosis of GHD. While it is possible that combining tests might yield different results from tests performed on separate days, there is no evidence against performing both tests sequentially on the same day."
- "2.2.2. Given the large discrepancies between GH assays, we recommend that institutions require laboratories to provide harmonized GH assays using the somatropin standard, IRP IS 98/574, 22k rhGH isoform, as recommended by the 2006 and 2011 consensus statements, and the published commutability standards. (Strong recommendation)"
- "3.5. We recommend that GH treatment at pediatric doses not continue beyond attainment of a growth velocity below 2–2.5 cm/year. The decision to discontinue pediatric dosing prior to attainment of this growth velocity should be individualized. (Strong recommendation)"
- "6.1 For children who meet DA criteria, 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)"
- "4.2. We recommend monitoring of GH recipients for potential development of intracranial hypertension, SCFE, and scoliosis progression by soliciting pertinent history and performing a physical examination at every follow-up clinic visit; further testing should be pursued if indicated. (Strong recommendation)"
- "4.3. We recommend re-assessment of both the adrenal and thyroid axes after initiation of GH therapy in patients whose cause of GHD is associated with possible multiple pituitary hormone deficiencies (MPHD). (Strong recommendation)"

For children with acquired GHD due to effects of a primary malignancy:

- "4.5.1.1.2. For GH initiation after completion of tumor therapy with no evidence of ongoing tumor, a standard waiting period of 12 months to establish "successful therapy" of the primary lesion is reasonable but can also be altered depending on individual patient circumstances. (Ungraded good practice statement). Although many of the intracranial tumors are not "malignant" (i.e., craniopharyngioma), they have the potential to recur. There are no data to suggest treating them differently than malignant tumors with regard to observation periods before initiating GH treatment."
- "4.5.1.2. In the rare situation where a child with GHD has an accompanying condition with intrinsic increased risk for malignancy (e.g., neurofibromatosis-1, Down syndrome, Bloom syndrome, Fanconi anemia, Noonan syndrome, and Diamond-Blackfan anemia), we recommend providing counseling regarding the lack of evidence concerning GH effect on malignancy risk in these groups. (Ungraded good practice statement)"

Transitional Care after Childhood GH Treatment

- "5.1. We recommend that patients with multiple (≥ 3) pituitary hormone deficiencies regardless of etiology, or GHD with a documented causal genetic mutation or specific pituitary/hypothalamic structural defect except ectopic posterior pituitary, be diagnosed with persistent GHD. (Strong recommendation)"
- "5.2. We recommend re-evaluation of the somatotropic axis for persistent GHD in persons with GHD and deficiency of only one additional pituitary hormone, idiopathic isolated GHD (IGHD), IGHD with or without a small pituitary/ectopic posterior pituitary, and in patients after irradiation. (Strong recommendation)- Testing can be performed after a trial of at least 1 month off GH treatment."
- "5.2.1. We suggest that measurement of the serum IGFI concentration be the initial test of the somatotropic axis if re-evaluation of the somatotropic axis is clinically indicated. (Conditional recommendation)"
- "5.2.2. We recommend GH provocative testing to evaluate the function of the somatotropic axis in the transition period if indicated by a low IGF-I level. (Strong recommendation)"
- "5.3. We suggest that GH treatment be offered to individuals with persistent GHD in the transition period. There is evidence of benefit; however, the specifics of the patient population that benefits, the optimal time to reinitiate treatment, and the optimal dose are not clear. (Conditional recommendation)- The transition period is the time from late puberty to establishment of adult muscle and bone composition and encompasses attainment of adult height (AH)."

GH Treatment of Patients with ISS:

"6.1. In the USA, for children who meet FDA criteria, we suggest a shared decision-making approach to pursuing GH treatment for a child with ISS. 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 (HtSDS) ≤ –2.25. (Conditional recommendation). While studies have shown GH treatment increases the mean height of treated cohorts, there is marked interindividual variability in responses, including some individuals who do not respond to treatment."

In 2024, the PES published practice guidelines on the management of Turner syndrome based on proceedings of the International Turner Syndrome Meeting. (81) The PES provided the following recommendations:

- "R 2.1 We recommend offering growth hormone (GH) treatment early, because growth failure in TS (turner syndrome) starts before birth and is rapid during the first years of life, and early GH treatment can prevent further loss of height potential. Treatment may be offered from as young as 2 years of age in the following circumstances: evidence of growth failure (rate of growth below normal or declining), short stature, or likelihood of short stature. GH treatment may be offered later, as long as epiphyses remain open (strong recommendation, moderate quality of evidence)."

- "R 2.2 We suggest that GH treatment may be continued until little growth potential remains (bone age ≥14 years and/or height velocity <2 cm year−1). There is no physiological rationale for continuing GH treatment into the transition period after epiphyseal closure (strong recommendation, moderate quality of evidence)."

American Association of Clinical Endocrinologists

In 2019, the American Association of Clinical Endocrinologists (AACE) updated its guidelines on GH use in GHD adults and patients transitioning from pediatric to adult care. (82) 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.

The AACE offers the following guidance specific to adults (82):

- "R12. After longitudinal growth is completed in transition patients with idiopathic isolated GHD, those with low-normal (between 0 to –2 SDS) or low (< –2 SDS) serum IGF-1 levels should be retested for GHD with GH–stimulation tests after at least 1 month following discontinuation of rhGH therapy (Grade B; BEL 4; upgraded by consensus based on expert opinion). "
- "R13. After longitudinal growth is completed in transition patients with isolated GHD (IGHD) and the presence of organic hypothalamic-pituitary disease (e.g., craniopharyngioma, pituitary hypoplasia, ectopic posterior pituitary, or previous cranial irradiation), the number of GH–stimulation tests to be undertaken should be guided by the degree of clinical suspicion for GHD. If clinical suspicion is high, 1 GH–stimulation test is sufficient, but if clinical suspicion is low, then a second GH–stimulation test should be performed (Grade B; BEL 4; upgraded by consensus based on expert opinion)"
- "R14. To continue rhGH replacement in adulthood, retesting for GHD with GH–stimulation test/s is recommended in most transition patients, especially patients with idiopathic isolated GHD and serum IGF-1 SDS <0, when longitudinal growth is complete, and at least 1 month after discontinuation of pediatric rhGH therapy (Grade A; BEL 1)."
- "R15. Patients with idiopathic IGHD and serum IGF-1 ≥0 SDS are likely to have a normal GH–stimulation test; hence, retesting and rhGH therapy in these patients after completion of longitudinal growth are not required (Grade C; BEL 2; downgraded due to inconsistent results)."
- "R16. Retesting is not required in transition patients with MPHD (≥3 PHD) and low-serum IGF-1 levels (<–2.0 SDS), patients with genetic defects affecting the hypothalamic-pituitary axes, and patients with hypothalamic-pituitary structural brain defects, and rhGH therapy

may be continued in these patients without interruption (Grade C; BEL 2; downgraded due to inconsistent results)."

- "R17. The risk for development of persistent GHD after radiation therapy is increased with higher radiation doses and longer duration of time since the therapy. Retesting those patients who initially test as GH–sufficient may be performed later in the transition period or in adulthood to rule out delayed GHD (Grade B; BEL 2)."
- "R18. TBI and subarachnoid hemorrhage are now recognized clinical conditions that may cause GHD, but because GHD may be transient in these patients, GH– stimulation testing should be performed only after at least 12 months following the event (Grade B; BEL 2)."
- "R19. Random serum GH and IGF-1 levels cannot be used alone to make the diagnosis of adult GHD, and GH–stimulation test/s should be performed to confirm the diagnosis with the exception of certain subpopulations, such as patients with organic hypothalamic-pituitary disease (e.g., suprasellar mass with previous surgery and cranial irradiation) who have MPHD (≥3 PHD) and low serum IGF-1 levels (<-2.0 SDS), patients with genetic defects affecting the hypothalamic-pituitary axes, and patients with hypothalamic-pituitary structural brain defects (Grade B; BEL 4; upgraded by consensus based on expert opinion)."
- "R20. GH–stimulation tests should only be performed after all other PHD have been optimally replaced with stable hormone replacement doses (Grade C; BEL 4; upgraded by consensus based on expert opinion)."
- "R21. The insulin tolerance test (ITT) remains the gold-standard test to establish the diagnosis of adult GHD using a peak GH cut-point of 5 μg/L. However, this test is increasingly used less frequently in the U.S. because of safety concerns, laboriousness, potential to cause severe hypoglycemia, and contraindicated in certain patients, such as elderly patients and those with seizure disorders and cardio/cerebrovascular disease. For adults suspected to have GHD and if the ITT is contraindicated or is not feasible to be performed in these patients, the glucagon-stimulation test (GST) and the macimorelin test could be considered as alternative tests (Grade B; BEL 1)."
- "R22. For the GST, we recommend utilizing BMI-appropriate GH cut-points to diagnose adult GHD to reduce the possibility of misclassifying GH-sufficient patients because increased BMI is associated with decreased glucagon-induced GH stimulatory effect. We recommend using the GH cut-point of 3 μg/L for normal-weight (BMI <25 kg/m$^{2)}$ and overweight (BMI 25 to 30 kg/m2) patients with a high pretest probability, and a lower GH cut-point of 1 μg/L for obese (BMI >30 kg/m$^{2)}$ and overweight (BMI 25 to 30 kg/m^2) patients with a low pretest probability. In patients with glucose intolerance, the diagnostic accuracy of the GST remains unclear (Grade B; BEL 2)."
- "R23. For the macimorelin-stimulation test, the U.S. Food and Drug Administration (FDA) approved this test for use as a diagnostic test for adult GHD in December, 2017, and selected the GH cut-point of 2.8 μg/L to differentiate patients with normal GH secretion from those with GHD. However, it is not yet known whether BMI-adjusted peak GH cut-points for this test are needed for over-weight and obese patients (Grade B; BEL 2)."
- "R24. For transition patients, a feasible and validated GH–stimulation test has been less well studied. In this patient population, the ITT (using a GH cut-point ≤5.0 μg/L) may be utilized, but if the test is contraindicated or not feasible to be performed, the GST (using a GH cut-

point of 3 µg/L for normal-weight [BMI <25 kg/m^2] patients and overweight [BMI 25 to 30 kg/m^2] patients with a high pretest probability, and a lower GH cut-point of 1 µg/L for overweight [BMI 25 to 30 kg/m^2] patients with a low pretest probability and obese [BMI >30 kg/m^2] patients) and the macimorelin test (using a GH cut-point ≤2.8 mg/L) can be considered as alternative tests (Grade C; BEL 2).

- "R25. Arginine (ARG) and levodopa (L-DOPA) testing have not been systematically evaluated and validated, and because these tests have low sensitivity and specificity in adults and transition patients with suspected GHD, we do not recommend utilizing these tests (Grade B; BEL 2)."

*Length of rhGH therapy: T*he appropriate length of rhGH therapy is unclear. If benefits are achieved, treatment can be continued indefinitely. But, if no apparent or objective benefits of treatment are achieved after at least 12-18 months, discontinuing rhGH therapy may be considered. If patients decide to discontinue rhGH replacement therapy, a 6-month follow-up is recommended, because some patients may wish to resume therapy, noting in retrospect that they did feel better on treatment.

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." (83)

Endocrine Society

In 2016, the Endocrine Society updated its practice guidelines on adult GHD included the following recommendation (84):

- 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 GH-deficient adults offers significant clinical benefits in body composition and exercise capacity.
- GH therapy for GH-deficient adults offers significant clinical benefits in skeletal integrity.

Separate Endocrine Society guidelines (2018) make the following recommendations for treatment of GHD in survivors of childhood cancer (85):

- 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) (86) statement indicates 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."

The GHRS (2013) issued consensus guidelines on human GH therapy for Prader-Willi syndrome (PWS). (87) 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 GH Safety Workshop were published in the *European Journal of Endocrinology*. (88) 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 (89) and noted:

- 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.

National Institute of Health and Care Excellence

In 2010, the National Institute of Health and Care Excellence (NICE) issued guidance on human GH for growth failure in children. (90) The Institute recommended GH as a possible treatment for children with growth failure with any of the following conditions:

- GHD;

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

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

Ongoing and Unpublished Clinical Trials
Currently ongoing or unpublished trials that might influence this policy are listed in Table 3.

Table 3. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Unpublished			
NCT03038594	Growth Hormone Therapy for Muscle Regeneration in Severely Burned Patients	64	Nov 2021 (completed)

NCT: national clinical trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	96372
HCPCS Codes	J2941, J3490, S9558

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

US Food and Drug Administration Labels:

1. FDA – Drugs @ FDA (FDA Approved Drug Products and Label Information. Available at <https://www.accessdata.fda.gov> (accessed September 17, 2025).
   - Genotropin® (somatropin) (July 2025);
   - Humatrope® (somatropin) (July 2025);
   - Norditropin® (somatropin) (July 2025);
   - Nutropin® (somatropin) (December 2016);
   - Omnitrope® (somatropin) (July 2025);

- Saizen® (somatropin) (May 2017);
- Serostim® (somatropin) (May 2017);
- Sogroya® (somatropin) (July 2025);
- Zomacton™ (somatropin) (July 2025);
- Zorbtive® (somatropin) (December 2023).

Other References:

2. 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. Aug 1998; 11(3):403-412. PMID 11517956
3. 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):2047-2054. PMID 16537676
4. Thornton PS, Maniatis AK, Aghajanova E, et al. Weekly Lonapegsomatropin in treatment-naive children with growth hormone deficiency: The phase 3 heiGHt trial. J Clin Endocrinol Metab. Oct 21 2021; 106(11):3184-3195. PMID 34272849
5. 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
6. Sävendahl L, Battelino T, Hojby 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
7. 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):2063-2071. PMID 18381581
8. Widdowson WM, Gibney J. The effect of growth hormone replacement on exercise capacity in patients with GH deficiency: A meta-analysis. J Clin Endocrinol Metab. Nov 2008; 93(11):4413-4417. PMID 18697875
9. 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):787-792. PMID 19769614
10. 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. May 2013; 2013:216107. PMID 23690770
11. 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):852-860. PMID 24423364
12. 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):2048-2056. PMID 15126520
13. Maison P, Chanson P. Cardiac effects of growth hormone in adults with growth hormone deficiency: A meta- analysis. Circulation. Nov 25 2003; 108(21):2648-2652. PMID 14623813

14. Sesmilo G, Biller BM, Llevadot J, et al. Effects of growth hormone administration on inflammatory and other cardiovascular risk markers in men with growth hormone deficiency. A randomized, controlled clinical trial. Ann Intern Med. Jul 18 2000; 133(2):111-122. PMID 10896637
15. 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):4657-4665. PMID 11600522
16. 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
17. 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
18. 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
19. 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
20. 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
21. 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
22. 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):129-133. PMID 22660958
23. Hodson EM, Willis NS, Craig JC. Growth hormone for children with chronic kidney disease. Cochrane Database Syst Rev. Feb 15 2012; 2(2):CD003264. PMID 22336787
24. Hokken-Koelega AC, Stijnen T, de Muinck Keizer-Schrama SM, et al. Placebo-controlled, chronic renal failure. Lancet. Sep 7 1991; 338(8767):585-590. PMID 1715501
25. 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):701-706. PMID 10912546
26. 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
27. 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

28. Juloski J, Dumancic J, Scepan I, et al. Growth hormone positive effects on craniofacial complex in Turner syndrome. Arch Oral Biol. Nov 2016; 71:10-15. PMID 27372203
29. 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. Feb 2015; 83(3):167-176. PMID 25721697
30. 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):1953-1956. PMID 11344190
31. 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
32. 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):219-228. PMID 17047016
33. 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
34. 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
35. 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 08 2023; 12(7):e220402. PMID 37014306
36. 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 1 2004; 37(Suppl 5):S262-S276. PMID 15722869
37. 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):301-303, 306-308, 310, 314. PMID 15962453
38. 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
39. 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. Nov-Dec 1999; 23(6):309-312; discussion 312-303. PMID 10574477
40. 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
41. 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

42. Maiorana A, Cianfarani S. Impact of growth hormone therapy on adult height of children born small for gestational age. Pediatrics. Sep 2009; 124(3):e519-531. PMID 19706577
43. 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):lvac008. PMID 36651161
44. 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
45. 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
46. 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
47. 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
48. 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):4873-4878. PMID 15472178
49. 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):507-515. PMID 12032514
50. 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):32-35. PMID 8813867
51. 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):1704-1710. PMID 8626820
52. 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):1868-1870. PMID 11344173
53. 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
54. 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
55. 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
56. 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
57. 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
58. 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
59. 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):416-425. PMID 22238382
60. Poidvin A, Touze 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):780-786. PMID 25122206
61. 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
62. 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
63. 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):526-530. PMID 7473919
64. Singh KP, Prasad R, Chari PS, et al. Effect of growth hormone therapy in burn patients on conservative treatment. Burns. Dec 1998; 24(8):733-738. PMID 9915674
65. Losada F, Garcia-Luna PP, Gomez-Cia 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
66. 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):827-834. PMID 11371741
67. 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):447-452. PMID 11451596
68. 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). Nov-Dec 2016; 48(11-12):829-837. PMID 27417288
69. 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):2099-2103. PMID 10546863
70. 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):1167-1178. PMID 27225286

71. 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): 928-932. PMID 10519330
72. Thaker V, Haagensen AL, Carter B, et al. Recombinant growth hormone therapy for cystic fibrosis in children and young adults. Cochrane Database Syst Rev. Jun 05 2013; 6(6):CD008901. PMID 23737090
73. Thaker V, Carter B, Putman M. Recombinant growth hormone therapy for cystic fibrosis in children and young adults. Cochrane Database Syst Rev. Dec 17 2018; 12:CD008901. PMID 30557452
74. Thaker V, Carter B, Putman M. Recombinant growth hormone therapy for cystic fibrosis in children and young adults. Cochrane Database Syst Rev. Aug 23 2021; 8:CD008901. PMID 34424546
75. Phung OJ, Coleman CI, Baker EL, et al. Recombinant human growth hormone in the treatment of patients with cystic fibrosis. Pediatrics. Nov 2010; 126(5):e1211-1226. PMID 20921071
76. Stalvey MS, Anbar RD, Konstan MW, et al. A multi-center controlled trial of growth hormone treatment in children with cystic fibrosis. Pediatr Pulmonol. Mar 2012; 47(3):252-263. PMID 21905270
77. Kaplowitz P, Bloch C, Sills IN, et al. Evaluation and referral of children with signs of early puberty. Pediatrics. Jan 2016; 137(1). PMID 26668298
78. Raman S, Grimberg A, Waguespack SG, et al. Risk of neoplasia in pediatric patients receiving growth hormone therapy--a report from the Pediatric Endocrine Society Drug and Therapeutics Committee. J Clin Endocrinol Metab. Jun 2015; 100(6):2192-2203. PMID 25839904
79. Grimberg A, Allen DB. Growth hormone treatment for growth hormone deficiency and idiopathic short stature: new guidelines shaped by the presence and absence of evidence. Curr Opin Pediatr. Aug 2017; 29(4):466-471. PMID 28525404
80. 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. Nov 2016; 86(6):361-397. PMID 27884013
81. 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. Jun 2024; 190(6):G53-151. PMID 38748847
82. 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
83. 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
84. 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

85. 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
86. 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):4210-4217. PMID 18782877
87. Deal CL, Tony M, Höybye C, et al. Growth Hormone Research Society workshop summary: Consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. J Clin Endocrinol Metab. Jun 2013; 98(6):E1072-1087. PMID 23543664
88. 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
89. 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
90. National Institute for Health and Care Excellence (NICE). Human growth hormone (somatropin) for growth failure in children [TA188]. 2010. Available at <https://www.nice.org.uk> (accessed September 19, 2025).
91. Yau M and Rapaport R. Growth Hormone Stimulation Testing: To test or not to test? That is one of the questions. Front Endocrinol (Lausanne) . Jun 9 2022; 13:902364. PMID 35757429

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
01/01/2026	Document updated. The following changes were made in coverage: 1) Separated coverage into FDA labelled indications versus off label indications; 2) Added section for contraindications for both label and off-label use; 3) Removed from the existing EIU statement under the off-label section a) Children born small for gestational age who fail to show catch-up growth by age 2 years; b) Children with height standard deviation score of -2.25 or

	below without documented growth hormone deficiency; c) Individuals with neurosecretory growth hormone dysfunction; d) Lipodystrophy [fat maldistribution] as an example of altered body habitus associated with antiviral therapy in HIV infected individuals; e) Intrauterine growth retardation; f) Treatment of advanced age or symptoms of aging; and g) Treatment of inflammatory bowel disease. Added reference 91; others updated and some removed.
09/15/2024	Document updated with literature review. The following change were made in Coverage: Updated term "patient" to "individual" throughout coverage. Added references 53, 67, and 112; others updated. Some removed.
10/15/2023	Document updated with literature review. The following changes were made in Coverage: 1) GHD in children: Moved documentation requirements from a note and incorporated it into coverage criteria. Moved partial GHD from the not medically necessary table to the GHD in children section as NOTE 3; 2) GHD in adults: Added macimorelin as an example of a provocative GH stimulation test. Reformatted language to clarify requirement of one failed provocative test in addition to select condition. Removed the parameter of <5 for provocative GH stimulation test. Added "with complete hypopituitarism" to state "Low concentration of insulin-like growth factor-1 (IGF-1) with complete hypopituitarism: 3) Moved the following statements from not medically necessary to experimental, investigational, and or unproven: a) children born small for gestational age who fail to show catch-up growth by age 2 years; b) children with height standard deviation score of -2.25 or below without documented growth hormone deficiency (see NOTE 14); and c) patients with neurosecretory growth hormone dysfunction 4) Changed term "patients" to "individuals" within coverage. Added reference 102, others updated/removed.
01/15/2023	Document updated with literature review. The following change was made in Coverage: Added ALERT 1: The Description section of this policy contains a listing of growth hormone preparations addressed by this policy. Coverage statements unchanged. Added Skytrofa® (lonapegsomatropin-tcgd) and Sogroya® (somapacitan-beco) to the list of growth hormone preparations in the Description. Added references 3, 6-10, 14, 19-21, 31, 33-35, 52, 70-96, 104, 111, 112 114, 118; some references revised; others removed.
02/01/2022	Document updated with literature review. The following change was made in Coverage: Revised the supportive documentation for growth hormone deficiency (GHD) in children Added reference 1.
03/01/2021	Reviewed. No changes.
10/15/2020	Document updated with literature review. The following changes were made to Coverage: 1) The term "growth" was replaced with "height" in the experimental, investigational and/or unproven statement to state "Constitutional delay (lower than expected height percentiles compared with their target height percentiles and delayed skeletal maturation when growth

	velocities and rates of bone age advancement are normal)"; 2) Added Note 10: Turner syndrome is defined as 45, XO genotype; 3) Added Note 12: Specialized nutritional support may consist of a high carbohydrate, low-fat diet, adjusted for individual patient requirements and preferences. Added references 11, 12, 24, 38, 72; some references removed.
06/15/2019	Reviewed. No changes.
07/15/2018	Document updated with literature review. The following was added in Coverage for patients with Prader-Willi syndrome: 1) With associated growth failure due to Prader-Willi syndrome, who do not have the following contraindications: history of upper airway obstruction or sleep apnea or severe respiratory impairment; and NOTE 11: Sleep studies are recommended prior to initiation of GH therapy for obese pediatric patients with Prader-Willi syndrome. If there are signs that upper airway obstruction and sleep apnea could occur, GH should not be administered. If during treatment, patients develop signs of upper airway obstruction or new sleep apnea, treatment should be interrupted. References 1-3, 8, 22-24, 29, 34, 36, 41, 58, and 64 added. Title changed from Growth Hormone.
04/15/2017	Document updated with literature review. Coverage unchanged.
02/15/2016	Reviewed. No changes.
07/15/2015	Document updated with literature review. The following coverage criteria were added to Growth hormone deficiency in children noted in the documentation of proven GHD section: central nervous system pathology; genetic defect (Refer to Turner's syndrome, Prader-Willi syndrome, or Noonan's syndrome). The following coverage criteria was added to Short-stature in children; proven SHOX (Short-stature homeobox-containing gene) deficiency. Rationale and References reorganized.
09/15/2012	Document updated with literature review. Coverage remains conditional based on meeting growth hormone deficiency criteria; clarified use in growth failure when used for Prader-Willi syndrome, inflammatory bowel disease, and advanced aging; and coverage added for Noonan's syndrome. Treatment of children with "genetic potential" (i.e., lower than expected height percentile based on parents' height) included as experimental, investigational and unproven. Clarified and expanded explanation of each FDA approved rhGH drug and their indication(s). CPT/HCPCS code(s) updated.
08/01/2007	Document updated with literature review.
03/23/2005	Document updated with coverage change.
06/01/2004	Document updated with coverage change.
12/01/2003	Document updated with literature review.
11/30/2003	Archived.
02/01/2002	CPT/HCPCS code(s) updated (*with bit changes*).
06/01/2001	CPT/HCPCS code(s) updated (*with bit changes*).
01/01/2000	Document updated with literature review.

02/01/1998	Document updated with literature review
05/01/1996	Document number changed.
04/01/1993	Document updated with literature review.
09/01/1990	New medical document.