Policy Number	**RX501.040**
Policy Effective Date	**09/15/2024**
Policy End Date	**12/31/2025**

Human Growth Hormone (GH)

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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 peer-reviewed scientific literature. 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 acceptable standards of medical practice. 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 HCSC 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.

Coverage

ALERT 1: The Description section of this policy contains a listing of growth hormone preparations addressed by this policy. This is not an all-inclusive listing of all growth hormone preparations. Refer to the U.S. Food and Drug Administration (FDA) for all labeled indications of those growth hormones not listed on this policy.

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

Growth hormone (GH) therapy is addressed by **specific indications and criteria** (see **Table 1** below). GH therapy **may be considered medically necessary** when:

- There is an FDA-approved labeled indication(s); **or**
- The FDA has granted an Orphan Drug Designation to the drug; **or**
- There is an off-label listing within a standard reference compendium (such as the American Hospital Formulary Service Drug Information [AHFS DI] or the Thompson Micromedex Drug Dex Compendium [Drug Dex]).

Table 1. MEDICALLY NECESSARY

If the FDA approved indication is:	**Then the criteria for review includes the following for medically necessary consideration:**
Growth hormone (GH) deficiency (GHD), **in children**	• Failed **TWO** provocative GH stimulation tests, each with peak value < 10 ng/ml. Testing can be done with growth hormone releasing hormone (GHRH), arginine, insulin, L-dopa, clonidine, or glucagon); **OR** • **Documentation** of proven GHD resulting from either: 1) A destructive lesion of the pituitary; 2) A medical treatment, including but not limited to ablative pituitary radiation or surgery; 3) Central nervous system pathology; 4) Genetic Defect (Refer to Turner's syndrome, Prader-Willi syndrome, or Noonan's syndrome below); or 5) Trauma; **AND** • 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, documented by the following: 1) Defined by age:

If the FDA approved indication is:	**Then the criteria for review includes the following for medically necessary consideration:**
	• Age 2-4 years: Pretreatment Height Velocity (HV) less than 5.5 cm/year (< 2.2 inches/year); • Age 4-6 years: Pretreatment HV less than 5 cm/year (< 2 inches/year); • Age 6 years to puberty AND ONE of the following: a. The individual is a boy and pretreatment HV is less than 4 cm/year (< 1.6 inches/year); OR b. The individual is a girl and pretreatment HV is less than 4.5 cm/year (< 1.8 inches/year) 2) The individual has a pretreatment bone age that is 2 SD below the mean. **NOTE 1:** In children, GH therapy is typically discontinued when the growth velocity is less than 2.0 cm/year; when epiphyseal fusion has occurred; or when the height reaches the 5th percentile of adult height. **NOTE 2:** Once GHD has been established in childhood no further documentation of need is required through age 18. **NOTE 3:** Individuals with partial GHD do not meet the criteria required for GHD, therefore further lab testing of children without classic GHD to diagnose partial GHD, or other abnormalities of GH secretion or bioactivity, is not medically necessary. This includes overnight hospitalization of children for testing of spontaneous GH secretion.
Short stature, **in children**	• Height less than 3rd percentile for chronological age **with** chronic renal insufficiency, with serum creatinine greater than 1.5 mg/dL, or a creatinine clearance less than or equal to 75 ml/minute per 1.73 m^2; **OR** • As a result of proven SHOX (short stature homeobox-containing gene) deficiency. **NOTE 4:** In pediatric individuals with chronic renal failure undergoing transplantation, GH therapy is discontinued at the time of transplant or when the growth velocity is less than 2.0 cm per year, when epiphyseal fusion has occurred, or when the height reaches the 5th percentile of adult height.
GHD, **in adults**	• Failed **TWO** provocative GH stimulation tests (e.g., insulin AND one of the growth hormone-releasing hormone preparations including arginine, L-dopa, clonidine, glucagon or macimorelin [macrilen™]) as an adult; **OR** • Failed **ONE** provocative GH stimulation tests (e.g., insulin or one of the growth hormone-releasing hormone preparations

If the FDA approved indication is:	Then the criteria for review includes the following for medically necessary consideration:
	including arginine, L-dopa, clonidine, glucagon or macimorelin [macrilen™]) as an adult; **AND documentation** of proven GHD resulting from either: 1) A destructive lesion of the pituitary; or 2) A medical treatment, including but not limited to ablative pituitary radiation or surgery; or 3) Central nervous system pathology; or 4) Genetic defect; or 5) Low concentration of insulin-like growth factor-1 (IGF-1) with complete hypopituitarism; **or** 6) Trauma. **NOTE 5:** Insulin Provocation is the preferred test 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, coronary artery disease, or high risk of coronary artery disease. **NOTE 6:** A provocation test using arginine and GHRH is also acceptable and is considered more stringent than tests using arginine alone or L-dopa alone. **NOTE 7:** Although an abnormal GH response has been traditionally defined as less than 10 ng/mL, different tests have different potencies, and the cutoff is likely to be lower when using monoclonal-based GH assays and RH-GH reference preparations. **NOTE 8:** Only about 25% of children with documented GHD will be found to have GHD when tested as adults. Therefore, once adult height has been achieved, individuals should be re-tested **ONE** time as adults to determine if continuing GH replacement therapy is medically necessary. **NOTE 9:** 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.
Acquired immunodeficiency syndrome (AIDS) wasting	• Weight loss greater than 10% of baseline weight (refer to **NOTE 10** below) that cannot be explained by a concurrent illness other than human immunodeficiency virus (HIV) infection; **AND** • Individual is on concurrent antiviral medications.

If the FDA approved indication is:	Then the criteria for review includes the following for medically necessary consideration:
	NOTE 10: GH therapy is discontinued when the loss is less than 10% of baseline weight loss.
Turner's syndrome	Associated growth failure. **NOTE 11:** Turner syndrome is defined as 45, XO genotype.
Prader-Willi syndrome	Associated growth failure, who do not have the following contraindications: • History of upper airway obstruction; or • History of sleep apnea; or • History of severe respiratory impairment. **NOTE 12:** 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, the individual develops signs of upper airway obstruction or new sleep apnea, treatment should be interrupted.
Noonan's syndrome	Associated growth failure.
Severe burns, **in children**	• 3rd degree burns to prevent growth delay when the treatment begins during acute hospitalization; **AND** • Up to one year after the 3rd degree burn, because scar tissue may interfere with growth.
Severe burns, **in adults**	3rd degree burns requiring promotion of wound healing.
Short bowel syndrome	• Treatment with specialized nutritional support in conjunction with optimal management of short bowel syndrome, including dietary adjustments, enteral feedings, parenteral nutrition, and fluid and micronutrient supplements. **NOTE 13**: Specialized nutritional support may consist of a high carbohydrate, low-fat diet, adjusted for individual patient requirements and preferences.

All label and off-label uses of any FDA approved drugs not included in the above medical necessity table **are considered experimental, investigational and/or unproven** as outlined in **Table 2** below when:

- The FDA has determined its use to be contraindicated for a specific condition; **or**
- The off-label uses cannot be validated by standard reference compendia or peer reviewed literature.

Table 2. EXPERIMENTAL, INVESTIGATIONAL and/or UNPROVEN

All Other Indications
Experimental, investigational and/or unproven indications for GH therapy include, but are not limited to, the following:

- Children born small for gestational age who fail to show catch-up growth by age 2 years;
- Children with height standard deviation score of -2.25 or below without documented growth hormone deficiency (see **NOTE 14**);
- Individuals with neurosecretory growth hormone dysfunction;
- 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);
- In conjunction with gonadotropin releasing hormone (GnRH) analogues as a treatment of precocious puberty;
- GH therapy in older adults (without proven GHD);
- 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's syndrome;
- Intrauterine growth retardation;
- Treatment of altered body habitus (e.g., buffalo hump, lipodystrophy [fat maldistribution]) associated with antiviral therapy in HIV infected individuals;
- Treatment of obesity;
- Treatment of cystic fibrosis (CF);
- Treatment of idiopathic dilated cardiomyopathy;
- Treatment of juvenile idiopathic- or juvenile chronic-arthritis;
- Treatment of advanced age or symptoms of aging;
- Treatment of inflammatory bowel disease; **OR**
- Treatment of children with "genetic potential" (i.e., lower than expected height percentile based on parents' height).

NOTE 14: The American Academy of Pediatrics (AAP) has pointed out that there will always be a population of individuals considered short based on the normal distribution of height, regardless of how the bell-shaped curve may be altered by GH therapy. The American Association of Clinical Endocrinologists and the Growth Hormone Research Society have defined "short stature" as a height more than 2 SDs below the mean for age and sex. (116) The FDA approved indication is for children with a height SD of -2.25 below the mean. (2, 110). Using this proposed definition, approximately 1.2% of all children would be defined as having idiopathic short stature (ISS).

The following diagnostic tests for GHD **are considered experimental, investigational and/or unproven**:

- 24-hour continuous monitoring of GH levels, OR
- Serum levels of insulin-like growth factor-binding protein (IGFBP).

Policy Guidelines

None.

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.

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

Traditionally, a more comprehensive evaluation of growth failure may be warranted in children when the height-for-age curve has deviated downward across two major height percentile curves (e.g., from above the 25th percentile to below the 10th percentile) or if the child is growing slower than the following rates:

- Age 2 to 4 years – Height velocity less than 5.5 cm/year (<2.2 inches/year);
- Age 4 to 6 years – Height velocity less than 5 cm/year (<2 inches/year);
- Age 6 years to puberty – Height velocity less than 4 cm/year for boys (<1.6 inches/year) or height velocity less than 4.5 cm/year for girls (<1.8 inches/year). (1)

In addition, there are ethical considerations regarding GH therapy, most prominently appropriate informed consent when the therapy is primarily requested by parents due to their particular psychosocial concerns regarding height.

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. GH products are utilized for a variety of U.S. Food and Drug Administration (FDA) labeled indications and the clinical evidence may not support differential effectiveness of one product over the other. The FDA approved indications and dosing vary based on each individual product therefore, the specific label and dosing should be reviewed.

This medical policy may not provide an all-inclusive list of GH preparations. Refer to the U.S. Food and Drug Administration (FDA) for all labeled indications for each GH product.

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

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

Some FDA approved GH products may include, but are not limited to the following preparations (2, 3):

- Genotropin® (somatropin injection);
- Humatrope® (somatropin injection);
- Ngenla® (somatrogon-ghla injection);
- Norditropin® (somatropin injection);
- Nutropin AQ® (somatropin injection);
- Omnitrope® (somatropin injection);
- Saizen® (somatropin injection);
- Serostim® (somatropin injection);
- Skytrofa® (lonapegsomatropin-tcgd);
- Sogroya® (somapacitan-beco);
- Zomacton® (somatropin injection) (In 2015, the FDA approved a name change for Tev-Tropin; Tev-Tropin is now known as Zomacton);
- Zorbtive® (somatropin injection).

In adult patients with GHD, the FDA has cautioned that the evidence on the safety and effectiveness of GH therapy in adults ages 65 and older is limited. Therefore, elderly patients may be more sensitive to the action of GH therapy and may be more prone to develop adverse events. (2)

Rationale

This policy was created in 1990 and has been updated regularly with searches of the PubMed database and standard reference compendiums through August 18, 2023. This policy focuses on the U.S. Food and Drug Administration (FDA) approved labeled indications and the off-label use of growth hormone (GH). The following discussion focuses on the most controversial aspects of GH 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 (GH) 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. (4-6) 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. (7) 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. (8) 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. (9) 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). (10) 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. (11) 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). (12) 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. (13) 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). (14) Data on outcomes of interest were prospectively collected from January 1985 through December 2014. For each case, 15 controls matched for sex, birth year, and geographical region were randomly selected from the Swedish Total Population Register (N=50,036). The primary outcome was the initial cardiovascular event recorded after the start of follow-up. Results revealed that a total of 1809 cardiovascular events were recorded during follow-up. The crude incidence rates were 25.6 (95% CI, 21.6 to 30.4) events per 10,000 person-years among GH patients and 22.6 (95% CI, 21.5 to 23.7) events per 10,000 person-years among controls. Among male patients and controls, the incidence rates were similar. However, the rate was higher in female GH patients than in female controls (31.2 events per 10,000 person-years vs. 23.2 events per 10,000 person-years). The authors concluded that GH treatment during childhood was associated with increased risks of cardiovascular events in early adulthood, particularly in women. However, a causal association is not definitively established, and the absolute risk remains low.

According to drug prescribing information, GH therapy use has been associated with sudden death in children with Prader-Willi syndrome. (15, 16) These deaths occurred among children who were severely obese or had severe respiratory impairment; these characteristics are now considered contraindications to GH treatment in patients with Prader-Willi syndrome.

Growth Hormone Deficiency (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 with proven GHD.

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

Populations

The relevant population of interest is individuals with proven GHD.

Interventions

The therapy being considered is human GH.

Comparators

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

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

GHD in Children
In children with GHD, treatment has been found to increase growth velocity and final height. Root et al. (1998) followed approximately 20,000 children for 9 years as part of the National Cooperative Growth Study. (17) Growth velocity improved compared with pretreatment values, and this improvement was maintained for at least 4 years. For children treated for at least 7 years, improvements in the mean height standard deviation score (SDS) ranged from 1.3 to 2.5, depending on the specific underlying condition. If treatment is started at an early age, most children can achieve a final height close to that expected from parental height. In a study of 1,258 patients in the Pfizer International Growth Database, Reiter et al. (2006) found the standard deviation (SD) for differences between the final height achieved and the midrange of predicted height from parental values ranged between -0.6 and +0.2, depending on the specific underlying condition. (18)

Once-weekly lonapegsomatropin in children was compared to daily somatropin in children with GHD in an open-label randomized trial. (19, 20) At the end of 2-year follow-up, height was improved by 1.37 to 2.89 SDS with lonapegsomatropin and 1.52 to 3.0 SDS with daily somatropin. At 104 weeks, bone age was minimally advanced relative to chronological age. Similarly, once-weekly somapacitan was compared to daily somatropin in children with GHD in a multicenter RCT. (21) After 3 years of follow-up, the mean height SDS was similar between treatment groups.

GHD in Adults
In adults with GHD, evidence from RCTs has shown that treatment leads to increases in lean body mass and decreases in body fat. (22)

Systematic Reviews
Meta-analyses of RCTs have shown evidence for increases in muscle strength and exercise capacity, although these findings were not robust across all studies. (23, 24) There is also evidence from meta-analyses that GH therapy is associated with increased bone mineral density (BMD) in adults with GHD. (25, 26) For example, a meta-analysis by Barake et al. (2014)

identified 9 placebo-controlled randomized trials with at least 1-year follow-up on the effect of daily GH therapy on BMD. (26) Analysis of RCT data found a statistically significant increase in BMD of the lumbar spine and femoral neck in patients with GHD who received GH therapy for more than 2 months. Change in BMD ranged from 1% to 5% at the spine and 0.6% to 4% at the femoral neck. A limitation of the Barakeet et al. (2014) analysis is that data were not available on fracture rates, a clinically important outcome. The evidence on other outcomes (e.g., QOL, lipid profiles, cardiovascular disease, total mortality) has been inconsistent and insufficient to determine whether these outcomes improved with treatment. (27-30) A meta-analysis of 5 studies (N=648) that compared long-acting GH and short-acting GH in adults with GHD found similar changes in lean mass, fat mass, and adverse events (including headache, arthralgia, and new-onset diabetes) between formulations. (31)

Observational Studies

Ishii et al. (2017) published an industry-funded, multicenter, observational study of GH therapy for adults with GHD. (32) One hundred sixty-one patients were eligible for QOL analysis using the Adult Hypopituitarism Questionnaire (AHQ). For male and female patients combined, AHQ scores were improved from baseline in both psycho-social and physical domains. Women had significantly lower AHQ scores than men throughout, however, the net changes in AHQ scores did not differ significantly between men and women (psycho-social domain: 4.90 vs 4.36; p=0.833; physical domain: 5.04 vs 2.29; p=0.213; respectively), despite an increase in GH dose such that insulin-like growth factor-1 levels for women reached that of men. The study was limited due to loss to follow-up, data collection being on patient recall, the observational design, and lack of a control group.

Section Summary: GHD Deficiency in Children and Adults

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

Short Stature Due to Prader-Willi Syndrome

Prader-Willi syndrome is a rare neurodevelopmental disorder characterized by muscular hypotonia, hypogonadism, short stature, obesity, psychomotor delay, neurobehavioral abnormalities, and cognitive impairment. Most children with Prader-Willi syndrome have hypothalamic dysfunction and are GH-deficient. The value of testing for GHD before treatment in these patients is questionable. None of the clinical studies selected patients for treatment based on the presence or absence of GHD, nor were results reported separately for those with or without GHD. Information from the product label indicates that the height SDS for Prader-Willi syndrome children in the clinical studies was -1.6 or less (height was in the tenth percentile or lower).

Clinical Context and Therapy Purpose

The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with short stature due to Prader-Willi syndrome.

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

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

Interventions
The therapy being considered is human GH.

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

Outcomes
The general outcomes of interest are functional outcomes, QOL, and treatment-related morbidity. Follow-up at 8 years is of interest to monitor outcomes.

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

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

Systematic Reviews
Frixou et al. (2021) completed a systematic review of 20 trials that evaluated the effects of GH in adults with Prader-Willi syndrome, primarily focusing on effects on body composition, bone, and cardiovascular health. (33) The included studies evaluated 424 subjects (51% male) with Prader-Willis syndrome; however, it is important to note that 60 subjects were recruited to more than 1 study, leaving 364 unique enrollees. The median (range) dose of GH administered in the studies was approximately 0.8 mg/day (0.5 to 1.0 mg/day) with a median duration of treatment of 1 year and median length of follow-up of 2 years. Overall, results revealed no differences in body mass index with GH therapy, although 2 studies noted an increased body mass index after GH treatment discontinuation. Statistically significant increases in lean body mass and decreases in percentage fat mass were seen with therapy. Inconsistent effects of GH on cholesterol and echocardiography parameters were also seen across studies. No differences in BMD were reported. GH therapy was well tolerated in adults with Prader-Willi syndrome;

however, further data are needed to evaluate the effects of GH on bone and cardiovascular health.

Luo et al. (2021) performed a meta-analysis of 10 RCTs (N=302) that evaluated the effects of GH on cognitive, motor, and behavioral development in children with Prader-Willi syndrome. (34) Results revealed no significant differences in cognitive performance (data from 6 RCTs) or objective assessments of behavioral development (data from 2 RCTs) between the GH treatment group and controls (p=.197 and p=.53, respectively). However, a significant improvement in motor development with GH therapy compared to control treatment (p<.001) was observed in data from 5 RCTs.

Passone et al. (2020) published a systematic review with meta-analysis evaluating GH treatment in patients with Prader-Willi syndrome. (35) Sixteen RCTs and 20 non-randomized trials were included in the review; controls included placebo or no treatment. Among patients enrolled in RCTs, treatment with GH significantly improved height (1.67 SDS; 95% CI, 1.54 to 1.81 SDS; n=322), body mass index z-scores (-0.67 SDS; 95% CI, -0.87 to -0.47SDS; n=119), fat mass proportion (-6.5% SDS; -8.46 to -4.54% SDS; n=204), and head circumference (mean difference [MD], 0.55 cm; 95% CI 0.25 to 0.86 cm; n=114) compared to control. Data regarding cognitive function, behavior, motor development, and QOL could not be pooled. However, improvements in cognition and motor development were demonstrated in small studies.

Randomized Controlled Trials

Other RCTs in children have shown improvements in health outcomes with GH treatment. For example, Kuppens et al. (2016) published results from a 2-year crossover, blinded, placebo-controlled randomized trial designed to investigate the effects of GH on body composition in young adults with Prader-Willi syndrome who were treated with GH during childhood and had attained adult height. (36) Patients (n=27) were stratified by sex and body mass index and randomized to GH injections once daily or placebo injections. After 1 year, the patients received the alternate treatment. Every 3 months, fat mass and lean body mass were measured by dual-energy x-ray absorptiometry. GH treatment resulted in lower mean fat mass (-17.3%) and higher lean body mass (+3.5%) compared with placebo.

Case Reports

There have been numerous case reports of sudden unexpected death in Prader-Willi syndrome patients undergoing GH therapy. (37-39) These deaths occurred among children who were severely obese or had severe respiratory impairment; these characteristics are now considered contraindications to GH treatment in patients with Prader-Willi syndrome. Furthermore, treatment should be discontinued if upper airway obstruction or sleep apnea occurs. (15, 16)

Section Summary: Short Stature due to Prader-Willi Syndrome

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

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

Short Stature Due to Chronic Renal Insufficiency

Clinical Context and Therapy Purpose

The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with short stature due to chronic renal insufficiency.

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

Populations

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

Interventions

The therapy being considered is human GH.

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Systematic Reviews

Wu et al. (2013) published a systematic review of RCTs evaluating the impact of GH therapy on height outcomes following a renal transplant in children ages 0 to 18 years. (40) Five trials (total n=401 participants) met reviewers' inclusion criteria (RCTs including renal allograft recipients between 0 and 18 years old). Trials were published between 1996 and 2002. A meta-analysis found significantly improved height velocity at the end of a trial in children taking GH compared

with a no-treatment control group. At the beginning of the year, both groups had a negative height SDS, with no statistically significant differences between groups. After 1 year, the pooled mean difference (MD) in height SDS was 0.68 (95% CI, 0.25 to 1.11; p=0.002) in favor of the GH group. There were no statistically significant differences between groups in the rate of rejection episodes or in renal function.

Previously, Hodson et al. (2012) published a Cochrane review of RCTs evaluating GH treatment in children with chronic kidney disease. (41) To be included in the review, trials needed to include children 18 years old or younger who were diagnosed with chronic kidney disease and were pre-dialysis, on dialysis, or posttransplant. In addition, trials had to compare GH treatment with placebo, no treatment, or a different GH regimen and needed to include height outcomes. Seven RCTs with 809 children met reviewers' criteria. Study entry criteria varied (e.g., ranging from <3rd percentile for chronologic age to <50th percentile for chronologic age). Overall, treatment with GH (28 IU/m^2/wk) compared with placebo or no specific therapy resulted in a statistically significant increase in height SDS at 1 year (8 studies; MD=0.82; 95% CI, 0.56 to 1.07). Moreover, a pooled analysis of 7 studies found a significant increase in height velocity at 1 year in the group receiving GH treatment compared with control (MD=3.88 cm/y; 95% CI, 3.32 to 4.44 cm/y).

Randomized Controlled Trials

An example of an individual RCT is Hokken-Koelega et al. (1991), conducted in the Netherlands. (42) This double-blind, placebo-controlled crossover trial included 20 prepubertal children with severe growth retardation and chronic renal failure. Entry criteria included height velocity less than the 25% percentile for chronologic age. Patients received 6 months of subcutaneous injection of GH (4 IU/m^2/d) before or after 6 months of placebo injection. There was a 2.9 cm greater increase in height velocity per 6 months with GH than with placebo. Long-term follow-up data on children in this and other Dutch RCTs (maximum of 8 years of treatment) were published in 2000. (43) GH treatment resulted in significant improvement in the height SDS compared with baseline scores (p<0.001). Moreover, the mean height SDS reached the lower end (-2 SDS) of the normal growth chart after 3 years of treatment. Puberty began at a median age within the normal range for girls and boys, and GH therapy did not significantly affect parathyroid hormone concentrations, and there were no radiologic signs of renal osteodystrophy.

Section Summary: Short Stature due to Chronic Renal Insufficiency

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

Short Stature Due to Turner Syndrome

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 short stature due to Turner syndrome.

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

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

Interventions
The therapy being considered is human GH.

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

Outcomes
The general outcomes of interest are functional outcomes, QOL, and treatment-related morbidity. Treatment of an average of 6 years is of interest to monitor outcomes.

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

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

Systematic Reviews
Li et al. (2018) conducted a meta-analysis to determine the effect of recombinant human GH treatment on height outcomes in patients with Turner syndrome. (44) Eleven RCTs (total n=1122 patients), published between 1986 and 2011, were identified for the analysis. Compared with controls, there was a significant increase in final height (MD, 7.2 cm; 95% CI, 5.27 to 9.18 cm; $p<0.001$), height SD (standardized mean difference [SMD], 1.22 cm; 95% CI, 0.88 to 1.56 cm; $p<0.001$), and height velocity (MD=2.68 cm/y; 95% CI, 2.34 to 3.02 cm/y; $p<0.001$) for patients receiving GH. After 1 year, bone age increased slightly for the GH group (standardized mean difference=0.32/y; 95% CI, 0.1 to 0.54/y; $p=0.004$). The meta-analysis was limited by the small number of available studies and the lack of sufficient data on final height.

A Cochrane review by Baxter et al. (2007) identified 4 RCTs (total n=365 patients) evaluating GH for treating Turner syndrome. (45) Studies included children who had not yet achieved final height, had treated children for at least 6 months, and compared GH with placebo or no treatment. Only 1 trial reported final height, so outcomes could not be pooled. A pooled analysis of 2 trials reported that short-term growth velocity was greater in treated than in untreated children (MD=3 cm/y; 95% CI, 2 to 4 cm/y).

Nonrandomized Studies

In addition to short stature, individuals with Turner syndrome also exhibit craniofacial characteristics such as shorter and flattened cranial bases and inclined maxilla and mandible. A cross-sectional study by Juloski et al. (2016) compared the craniofacial morphology of 13 patients who had Turner syndrome treated using GH with 13 patients who had Turner syndrome not treated using GH. (46) Mean age of participants was 17 years. Individuals in the treatment group had received GH for a mean of 5.8 years. Comparisons of lateral cephalometric radiographs showed that GH therapy significantly increased linear measurements, mainly influencing posterior and anterior face height, mandibular height and length, and maxillary length. Angular measurements and facial height ratio did not differ significantly between groups.

Section Summary: Short Stature due to Turner Syndrome

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

Short Stature Due to Noonan Syndrome

Clinical Context and Therapy Purpose

The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with short stature due to Noonan syndrome.

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

Populations

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

Interventions

The therapy being considered is human GH.

Comparators

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

Outcomes

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

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

Giacomozzi et al. (2015) published a systematic review of literature on the effect of GH therapy on adult height. (47) Included in the review were studies treating individuals with a diagnosis of Noonan syndrome with no other causes of short stature and a normal karyotype in females. In addition, studies had to follow patients for at least 3 years. Twenty-three studies were identified in a literature search conducted through April 2014, and 6 studies (total n=177 patients) met the inclusion criteria; none were RCTs, 1 was controlled, and the rest prospective or retrospective cohort studies or case reports. To summarize, in the controlled study by MacFarlane et al. (2001) (48), the GH-treated group gained a mean of 3.3 cm more than the untreated group over a 3-year follow-up. Among uncontrolled studies, 2 reported adult height. Mean height SDS was -2.8 (SD=0.6) and mean adult height SDS was -1.4 (SD=0.9). Two uncontrolled studies reported near-adult height, which was -2.1 (SD=0.9). In addition, 2 studies reported a change in height SDS corresponding to 8.6 cm (SD=5.9). Mean gain in height in SDS ranged from 0.6 to 1.4 cm by national standards, and between 0.6 and 2.0 cm by Noonan standards. The data were limited by the paucity of controlled studies and the lack of RCTs.

Section Summary: Short Stature due to Noonan Syndrome

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

Short Stature due to Short Stature Homeobox-Containing Gene (*SHOX)* Deficiency

Clinical Context and Therapy Purpose

The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with short stature due to short stature homeobox-containing gene (*SHOX)* deficiency.

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

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

Interventions
The therapy being considered is human GH.

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

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

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

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

Randomized Controlled Trials
A health technology assessment by Takeda et al. (2010) assessed GH treatment of growth disorders in children identified an RCT evaluating GH therapy for children with short stature due to *SHOX* deficiency. (49) This industry-sponsored, open-label multicenter trial was published by Blum et al. (2007). (50) It included 52 prepubertal children age at least 3 years who had *SHOX* deficiency. Height requirements were less than the 3rd percentile of the local reference range or less than 10th percentile with height velocity less than the 25th percentile. Participants were randomized to 2 years of GH treatment (n=27) or usual care (n=25). The primary outcome was first-year height velocity. Fifty-one of 52 patients completed the trial. The first-year height velocity was 8.7 cm/y in the GH therapy group and 5.2 cm/y in the usual care group ($p<0.001$). Height gain over the 2-year treatment period was 16.4 cm in the treatment group and 10.5 cm in the usual care group ($p<0.001$). No serious adverse events were reported for either group. At the end of the randomized phase, all patients were offered GH.

Nonrandomized Studies
Benabbad et al. (2017) published long-term height results and safety data from patients in the Blum et al. (2007) RCT (described above) and from a subset of patients with short stature due to *SHOX* deficiency from the Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS). (51) GeNeSIS was a prospective, multinational, open-label, pediatric surveillance program examining long-term safety and efficacy of GH. The subset of the GeNeSIS

population with *SHOX* deficiency consisted of 521 patients. Forty-nine of the 52 patients in the RCT enrolled in the long-term study. Patients in both studies will be followed until they achieve near-adult (final) height. Final height was defined as attaining 1 of the following criteria: height velocity less than 2 cm/y, hand x-ray showing closed epiphyses, or bone age older than 14 years for boys or older than 16 years for girls. At the time of the analysis, 90 patients from GeNeSIS and 28 patients from the RCT reached near-adult height. For the GeNeSIS patients, mean age at GH treatment initiation was 11.0 years, mean age at near-adult height was 15.7 years, and GH treatment duration was 4.4 years. For the RCT patients, mean age at GH initiation was 9.2 years, mean age at near-adult height was 15.5 years, and GH duration was 6.0 years. The most common treatment-emergent adverse events reported in the GeNeSIS patients were precocious puberty (2.6%) and arthralgia (2.4%). The most common treatment-emergent adverse events reported in the RCT patients were headache (18.4%) and congenital bowing of long bones (18.4%).

The final results of the GeNeSIS study (mean duration of follow-up 4.2 years; and mean duration of treatment 4.9 years) found that the most common treatment-emergent adverse events reported for patients with *SHOX* deficiency continued to be precocious puberty (3%) and arthralgia (2.8%). (52)

Bruzzi et al. (2023) published an Italian retrospective cohort study that reported anthropometric data from children and adolescents (N=117) with SHOX deficiency who were treated with GH and followed for up to 4 years. (53) The study found that growth velocity and height significantly improved during GH treatment. A multiple regression analysis also identified that the main independent predictor factors of height gain were the age at the start of GH treatment (p=.030) and growth velocity during the first year of therapy (p=.008).

Section Summary: Short Stature due to *SHOX* Deficiency

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

Severe Burns

Clinical Context and Therapy Purpose

The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in 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. (54) 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. (55) 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%). (56) 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. (57)

Prevention of Growth Delay in Children with Severe Burns

Children with severe burns show significant growth delays for up to 3 years after injury. GH treatment in 72 severely burned children for 1 year after discharge from intensive care resulted in significantly increased height in a placebo-controlled, randomized, double-blinded trial. (58) 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. (59)

Section Summary: Severe Burns

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

Acquired Immunodeficiency Syndrome (AIDS) Wasting

Clinical Context and Therapy Purpose

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

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

Populations

The relevant population of interest is individuals with AIDS wasting.

Interventions

The therapy being considered is human GH.

Comparators

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

Outcomes

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

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

Moyle et al. (2004) published a systematic review and meta-analysis of controlled and uncontrolled studies on selected treatments of HIV wasting. (60) To be included, studies had to assess more than 10 patients and have a treatment duration lasting at least 2 weeks. Pooled analysis of 3 studies using GH therapy showed significant increases in lean body mass compared with placebo (MD=3.1; 95% CI, 2.7 to 3.6). Pooled analysis of 6 studies reporting pre-post lean body mass measurements also showed significant increases following GH treatment (MD=2.7; 95% CI, 1.4 to 3.7). Lastly, 2 studies found statistically significant improvements in some measurements of QOL after 12 weeks with GH treatment.

Randomized Controlled Trials

A double-blind RCT by Evans et al. (2005) included 700 patients with HIV-associated wasting. (61) Patients were randomized to daily GH, alternate days of GH, or placebo. Patients assigned to daily GH had significantly greater increases in maximum exercise capacity (the primary outcome) than patients assigned to placebo.

Section Summary: AIDS Wasting

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

Short Bowel Syndrome with Specialized Nutritional Support

Clinical Context and Therapy Purpose

The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with short bowel syndrome on specialized nutritional support.

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

Populations

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

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

Interventions
The therapy being considered is human GH.

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

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

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

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

Systematic Reviews
A Cochrane review by Wales et al. (2010) identified 5 RCTs evaluating GH therapy for treating short bowel syndrome. (62) Studies evaluated GH with or without glutamine treatment. The primary outcome was change in body weight. A pooled analysis of 3 small trials (n=30 patients) found a statistically significant difference in weight change when patients were treated with GH compared with placebo (MD=1.7 kg; 95% CI, 0.7 to 2.6 kg; $p<0.001$). Lean body mass, nitrogen absorption, and energy absorption also significantly increased in patients receiving GH therapy compared with controls.

Several published trials have also demonstrated improved intestinal absorption in short bowel syndrome patients receiving parenteral nutrition. (63, 64) However, the Cochrane review and the studies noted that the effects of increased intestinal absorption were limited to the treatment period. (62, 64, 65) Specialized clinics may offer intestinal rehabilitation for patients with short bowel syndrome; GH may be a component of this therapy.

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

bowel syndrome; other studies have found improved intestinal absorption during GH therapy in patients with short bowel syndrome receiving parenteral nutrition.

Small for Gestational Age Children

Clinical Context and Therapy Purpose

The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals who are small for gestational age in childhood.

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

Populations

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

Interventions

The therapy being considered is human GH.

Comparators

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

Outcomes

The general outcomes of interest are functional outcomes, QOL, and treatment-related morbidity. Treatment of an average of 7.3 years is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Systematic Reviews

A meta-analysis of RCTs evaluating GH treatment for children born small for gestational age was published by Maiorana and Cianfarani (2009). (66) Four trials (N=391) met selection criteria (birth height or weight <2 SDS, initial height <2 SDS). The GH dose ranged from 33 to 67 µg/kg in the RCTs, and the mean duration of treatment was 7.3 years. Mean adult height in the 4 studies was -1.5 SDS in the treated group and -2.4 SDS in the untreated group. Adult height in the treated group was significantly higher than that of controls (MD=0.9 SDS [5.7 cm]; p<0001). There was no difference in adult height between the 33 and 67 µg/kg/d doses. Reviewers noted that it is unclear whether the gain in adult height associated with GH treatment "is of sufficient

clinical importance and value to warrant wide-spread treatment of short children born SGA [small for gestational age] …."

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

Randomized Controlled Trial

Juul et al. (2023) compared once weekly somapacitan with daily GH in a multicenter, open-label trial that included 62 prepubertal short children born small for gestational age (Table 3). (67) The main study period was 26 weeks, followed by a 26-week extension, a 4-year safety extension (ongoing), and a 30-day follow-up period. In the first year, the study was designed as a 5-arm, parallel-group study with 3 doses of somapacitan (0.16, 0.20, or 0.24 mg/kg/week) and 2 doses of daily GH (0.035 or 0.067 mg/kg/day). Thereafter, all participants were switched to a single somapacitan dose. The primary outcome, mean annualized height velocity (cm/y) at 26 weeks, was 8.9, 11.0, and 11.3 cm/y for somapacitan 0.16, 0.20, and 0.24 mg/kg/week, respectively, and 10.3 and 11.9 cm/y for daily GH 0.035 and 0.067 mg/kg/day, respectively. A dose-dependent response was confirmed with all treatments and there were no statistically significant differences in height velocity between somapacitan and daily GH (Table 4).

Table 3. Summary of Key RCT Characteristics

Study; Trial	**Countries**	**Sites**	**Dates**	**Participants**	**Interventions**	
					Active	*Comparator*
Juul et al. (2023) (67)	US, EU, Asia	38	July 2019 to May 2021	62 prepubertal short children born small for gestational age	Once weekly somapacitan (0.16, 0.20, or 0.24 mg/kg/week)	Daily GH (0 067 mg/kg/day)

EU: European Union; GH: growth hormone; RCT: randomized controlled trial; US: United States.

Table 4. Summary of Key RCT Results

Study	**ETD (95% CI) for height velocity (cm/y) at 26 weeks**
Juul et al. (2023) (67)	N=62
Somapacitan 0.16 mg/kg/week vs GH 0.035 mg/kg/day	−1.4 (−3.2 to 0.4)
Somapacitan 0.20 mg/kg/week vs GH 0.035 mg/kg/day	0.7 (−1.1 to 2.5)

Somapacitan 0.20 mg/kg/week vs GH 0.067 mg/kg/day	−0.9 (−2.6 to 0.9)
Somapacitan 0.24 mg/kg/week vs GH 0.067 mg/kg/day	−0.6 (−2.4 to 1.2)

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

The purpose of the study limitations tables (see Tables 5 and 6) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 5. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Juul et al. (2023) (67)			5. No true comparator (all groups received treatment with GH)		

GH: growth hormone.

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

[e] Follow-Up key: 1. Not sufficient duration for benefit 2. Not sufficient duration for harms; 3. Other.

Table 6. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Juul et al. (2023) (67)		1, 2. Open-label study				

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Small for Gestational Age Children

For individuals who are small for gestational age in childhood who receive human GH, the evidence includes a RCT and meta-analysis of RCTs. The RCT compared once-weekly GH therapy (somapacitan) with daily GH therapy in prepubertal short children born small for gestational age (N=62) and found no statistically significant difference in height velocity between treatments at 26 weeks. The meta-analysis found that GH treatment in small for gestational age children resulted in significantly greater adult height compared with no treatment; however, the clinical significance of the height difference between the study groups is unclear. There are few data on psychological or functional outcomes associated with this additional gain in height.

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 an 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 Idiopathic Short Stature (ISS)
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 children with idiopathic short stature (ISS).

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

Populations
The relevant population of interest is children with ISS (without documented GHD or underlying pathology).

Interventions
The therapy being considered is human GH.

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

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

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

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- 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.

Impact on Adult Height
Systematic Reviews
Various meta-analyses have assessed the impact of GH on ISS and adult height. Table 3 presents a crosswalk of included trials in these meta-analyses and Table 7 summarizes characteristics of these publications. A Cochrane review by Bryant et al. (2007) evaluated GH therapy for ISS in children and adolescents. (70) Ten RCTs met eligibility criteria; 3 studies were placebo-controlled, and the other 7 compared GH therapy with no treatment. Unlike the Deodati and Cianfarani (2011) review (described next), studies were not required to report final adult height. Nine of 10 studies in the Cochrane review were short term and reported intermediate outcomes. A pooled analysis of 3 studies reporting growth velocity at 1 year found a statistically significant greater growth velocity in treated than in untreated children (Table 9). Five studies reported height SDS, but there was heterogeneity among studies, and findings were not pooled. These data would suggest that GH has an effect on height in children with ISS in the short term but that evidence on GH's effects on adult height is limited.

Deodati and Cianfarani (2011) identified 3 RCTs and 7 non-RCTs in their systematic review. (71) Adult height was defined as a growth rate of <1.5 cm/year or bone age of 15 years in females and 16 years in males. The primary efficacy outcome was the difference between groups in adult height, measured as SDS. The investigators considered an MD in height of more than 0.9 SDS (≈6 cm) to be a satisfactory response to GH therapy. Only 1 randomized trial was placebo-controlled, and that trial had a high dropout rate (40% in the treated group, 65% in the placebo group). Table 6 represents results of the analysis. Although GH treatment resulted in a statistically significant increase in adult height in the treated group, according to the *a priori* definition of a satisfactory response (difference, 0.9 SDS), the difference was not clinically significant. Moreover, there was a lack of high-quality, placebo-controlled randomized trials.

Paltoglou et al. (2020) also evaluated the effect of GH therapy on linear growth and adult height in children with ISS. (72) This analysis included 21 studies: 10 studies examined the short-term effect of GH on linear growth, while 11 examined the effect of GH treatment on adult height. Overall, 11 of the included trials were randomized (1 trial was double-blind and placebo-controlled) while 10 lacked randomization. Results are presented in Table 9. Overall, children administered GH had a significantly higher height increment at the end of the first and second years of treatment and also achieved significantly higher adult height than the control group. However, the authors acknowledged that their findings indicate "that further studies are required to evaluate the effect of GH treatment in idiopathic short stature" and that "studies of improved quality, larger sample size and properly randomized would be invaluable in elucidating the effect of GH on adult height, as well as the optimal required doses."

Table 7. Comparison of Trials Included in Systematic Reviews and Meta-Analyses

Study	**Paltoglou et al. (2020) (72)**	**Deodati and Cianfarani (2011) (71)**	**Bryant et al. (2007) (70)**
Genentech (1989) (73)	X		X
Ackland et al. (1990) (74)			X
Cowell et al. (1990) (75)			X
Leschek et al. (2004) (76)	X	X	X
McCaughey et al. (1994) (77)	X		X
Barton et al. (1995) (78)			X
Soliman et al. (1996) (79)	X		X

Kamp et al. (2002) (80)	X		X
Volta et al. (1993 (81)	X		X
McCaughey et al. (1998) (82)	X	X	X
Albertsson-Wikland et al. (2008) (83)	X	X	
Hindmarsh et al. (1987) (84)	X		
Wit et al. (1989) (85)	X		
Volta et al. (1991) (86)	X		
Lanes et al. (1995) (87)	X		
Tao et al. (2015) (88)	X		
Zadik et al. (1992) (89)	X		
Wit et al. (1995) (90)	X	X	
Hindmarsh et al. (1996) (91)	X	X	
Buchlis et al. (1998) (92)	X	X	
Lopez-Siguero et al. (2000) (93)	X	X	
Coutant et al. (2001) (94)	X	X	
Wit et al. (2002) (95)	X	X	
van Gool et al. (2010) (96)	X		
Lopez-Siguero et al. (1996) (97)		X	

Table 8. Systematic Reviews and Meta-Analyses Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Bryant et al. (2007) (70)	1980-2006	10	Children with idiopathic short stature and with normal GH secretion, defined as a GH level above 7 µg/L	633 (18-121)	RCTs	For short term outcomes: GH had to be given for a minimum of 6 months; for final height outcomes, GH had to be given

			following a stimulation test			until final height achieved.
Deodati and Cianfarani (2011) (71)	1985-2010	10	Patients with initial short stature, defined as height >2 SDS below the mean; peak GH responses >10µg/L; prepubertal state; no previous GH therapy; and no comorbid conditions that would impair growth	592 (14-121)	RCTs (n=3); Non-RCTs (n=7)	Mean duration of therapy was 5.4 yrs.
Paltoglou et al. (2020) (72)	1985-2017	21	Children with short stature (height <2 SDS AND no previous GH treatment)	965 (12-335)	RCTs (n=11); Non-RCTs (n=10)	GH treatment for > 6 mos.

GH: growth hormone; RCT: randomized controlled trial; SDS: standard deviation score; yrs: years; mos: months.

Table 9. Systematic Review and Meta-Analysis Results

Study	Mean Adult Height (RCTs)	Mean Adult Height (Non-RCTs)	Growth Velocity at 1 Year	Height at End of First and Second Years of Treatment	Effect on Adult Height
Bryant et al. (2007) (70)					
Number of Studies			N=3		
WMD (95% CI)			2.48 (2.06 to 2.90)		
Deodati and Cianfarani (2011) (71)					
Total N	115	477			
SDS GH-Treated Children	-1.52	-1.7			
SDS Untreated Children	-2.30	-2.1			

MD (95% CI)	0.65 (0.40 to 0.91 SDS)	0.45 (0.18 to 0.73 SDS)			
p-value	<.001	<.001			
Paltoglou et al. (2020) (72)					
Total N				140 (4 studies; 1st year) 133 (3 studies; 2nd year)	573 (11 studies)
SMD (95% CI)				0.96 (0.26 to 1.66) 2.37 (1.48 to 3.26)	1.05 (0.68 to 1.42)
p-value				<.05 <.001	<.001

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

Impact on Self-Esteem and Quality of Life

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

Randomized Controlled Trials

Shemesh-Iron et al. (2019) published a 1-year blinded RCT and 3-year open-label study evaluating GH therapy in 60 prepubertal boys with ISS (mean age, 10 years). (98) During the blinded phase, patients were randomized to GH therapy (n=40) or placebo (n=20), and in the open-label phase, all patients received GH therapy (n=58). After 1-year, GH therapy significantly improved actual and anticipated adult height perception based on the Silhouette Apperception Test (SAT) (p<.001 and p=.022, respectively) and reduced short stature-related distress based on the Single-Category Implicit Association Test for height (SC-IAT-H; p<.001). After 4-years, GH therapy significantly improved scores on the Rosenberg Self-Esteem Scale (RSES) and SC-IAT-H (p<.001 for both), but there were no significant changes in the Pediatric Quality of Life Inventory (PedsQL) and Child Behavior Checklist (CBCL) scores.

Ross et al. (2004) published findings on psychological adaptation in 68 children with ISS without GHD. (99) Children (mean age, 12.4 years) were randomized to GH therapy (n=37) or placebo (n=31) 3 times per week until height velocity decreased to less than 1.5 cm/year. At baseline and then yearly, parents and children completed several psychological instruments including the Child Behavior Checklist (CBCL) and the Self-Perception Profile. No significant associations were found between attained height SDS or change in height SDS and annual changes in CBCL scores. There were no significant differences between groups on any CBCL summary scales in years 1 and 2, but, in year 4, there were significantly higher scores on the CBCL summary scales

in the group receiving GH treatment. There were no significant differences between groups on the Self-Perception Profile at any follow-up point. This trial did not find a correlation between short stature and psychological adaptation or self-concept.

Theunissen et al. (2002) in the Netherlands published a trial in which 40 prepubertal children with ISS were randomized to GH treatment (n=20) or a control group (n=20). (100) Parents and children were interviewed at baseline and at 1 and 2 years to obtain information on health related QOL and children's self-esteem. At the 2-year follow-up, satisfaction with current height was significantly associated with improvement in children's reported health-related QOL, social functioning, and other psychosocial measures. However, satisfaction with height did not differ significantly between the treatment and control groups. The data from this trial did not support the hypothesis that GH treatment improves health related QOL in children with idiopathic short stature.

Downie et al. (1996) examined the behavior of children without documented GHD who were treated with GH due to ISS. (101) Across measures of behavior, including IQ, self-esteem, self-perception, or parental perceptions of competence, there were no significant differences between the control and the treatment groups, either at baseline or after 5 years of GH therapy. The authors concluded that while no psychosocial benefits of GH therapy have been demonstrated, likewise, no documented psychosocial ill effects of GH treatment have been demonstrated.

Section Summary: Children with Idiopathic Short Stature

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

Children With "Genetic Potential"

Clinical Context and Therapy Purpose

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

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

Populations

The relevant population of interest is children 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 children 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 children 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. (102) 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. (103) 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 children 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.

Liu et al. (2007) stated that human GH is sometimes used as anti-aging therapy, although its use for this purpose has not been approved by the U.S. FDA and its distribution as an anti-aging agent is considered illegal in the U.S. Liu and colleagues evaluated the safety and effectiveness of GH therapy in the healthy elderly. They found that the literature published in RCTs evaluating GH therapy in the healthy elderly is limited but suggests that it is associated with small changes in body composition with increased rates of adverse events. The authors concluded that based on evidence, GH cannot be recommended as anti-aging therapy. (104)

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. (105) 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. (106) 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. (107)

Previously, a systematic review by Phung et al. (2010) identified 10 controlled trials evaluating GH for treating patients with CF. (108) 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). (109) 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

Growth Hormone Deficiency (GHD)

For individuals who have proven Growth Hormone Deficiency (GHD) who receive human GH, the evidence includes randomized controlled trials (RCTs), large observational studies, and meta-analyses. Relevant outcomes are functional outcomes, quality of life (QOL), and treatment-related morbidity. Studies have found that, for patients with documented GHD and clinical manifestations such as short stature, GH replacement improves growth velocity and final height achieved. In addition, studies have shown that GH therapy can ameliorate the secondary manifestations of GHD such as an increase in lean muscle mass and bone mineral density seen primarily in older children and adults. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Short Stature due to Prader-Willi Syndrome

For individuals who have short stature due to Prader-Willi syndrome who receive human GH, the evidence includes a systematic review, meta-analyses, a RCT and case reports. Relevant outcomes are functional outcomes, QOL, and treatment-related morbidity. A systematic

review, meta-analyses, and a RCT have found improvements in height, body mass index, body composition, head circumference, and motor development in children with Prader-Willi syndrome treated with GH. Case reports have found an increased risk of adverse events, including death, in patients with Prader-Willi syndrome who are severely obese or have a severe respiratory impairment; these characteristics are now considered contraindications to GH treatment in patients with Prader-Willi syndrome. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Short Stature due to Chronic Renal Insufficiency

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

Short Stature due to Turner Syndrome

For individuals who have short stature due to Turner syndrome who receive human GH, the evidence includes meta-analyses of RCTs and an observational study. Relevant outcomes are functional outcomes, QOL, and treatment-related morbidity. The available data have shown that GH therapy increases height outcomes (e.g., final height, height velocity) and positively affects craniofacial development in children with short stature and craniofacial complex due to Turner syndrome compared with placebo or no treatment. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Short Stature due to Noonan Syndrome

For individuals who have short stature due to Noonan syndrome who receive human GH, the evidence includes a systematic review of controlled and uncontrolled studies. Relevant outcomes are functional outcomes, QOL, and treatment-related morbidity. While the studies in the systematic review were generally of low quality and included only 1 trial comparing patients receiving GH with patients receiving no treatment, reviewers found that GH therapy was associated with an increase in height in patients with Noonan syndrome. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Short Stature due to Short Stature Homeobox-Containing Gene (*SHOX*) Deficiency

For individuals who have short stature due to short stature homeobox-containing gene (*SHOX*) deficiency who receive human GH, the evidence includes a RCT and long-term observational studies. Relevant outcomes are functional outcomes, QOL, and treatment-related morbidity. The RCT found that children with short stature due to *SHOX* deficiency had significantly greater height velocity and height gain after 2 years when treated with GH than with no GH. The long-term studies reported that, after 4 to 6 years of GH treatment, patients with *SHOX* deficiency

may attain near-adult height. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Severe Burns

For individuals who have severe burns who receive human 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 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.

Acquired Immunodeficiency Syndrome (AIDS) Wasting

For individuals who have AIDS wasting who receive human GH, the evidence includes a meta-analysis and RCT. Relevant outcomes are functional outcomes, QOL, and treatment-related morbidity. The meta-analysis found significant improvements in lean body mass and QOL with GH therapy versus placebo. A RCT with a large sample size reported a significantly greater increase in exercise capacity with GH than with placebo. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Short Bowel Syndrome with Specialized Nutritional Support

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

Small for Gestational Age Children

For individuals who are small for gestational age in childhood who receive human GH, the evidence includes a RCT and meta-analysis of RCTs. Relevant outcomes are functional outcomes, QOL, and treatment-related morbidity. The RCT compared once-weekly GH therapy (somapacitan) with daily GH therapy in prepubertal short children born small for gestational age (N=62) and found no statistically significant difference in height velocity between treatments at 26 weeks. The meta-analysis found that GH treatment in small for gestational age children resulted in significantly greater adult height compared with no treatment; however, the clinical significance of the height difference between the study groups is unclear. There are few data on the psychological or functional outcomes associated with this additional gain in height. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Altered Body Habitus Related to Antiretroviral Therapy For Human Immunodeficiency Virus (HIV) Infection

For individuals who have altered body habitus related to antiretroviral therapy for HIV infection who receive human GH, the evidence includes an RCT and case series. Relevant outcomes are functional outcomes, 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.

Children with Idiopathic Short Stature

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

Children with "Genetic Potential"

For individuals who have "genetic potential" (i.e., lower than expected height percentiles based on parents' height) who receive human GH, 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.

Precocious Puberty

For individuals who have precocious puberty who receive human GH plus gonadotropin-releasing hormone (GnRH), the evidence includes a meta-analysis and 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-analyses of final height, the difference in final height and targeted height, and height gain. The meta-analyses 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.

Older Adults with Age-Related GHD

For individuals who are older adults with age-related GHD who receive human GH, no clinical trials evaluating GH therapy were identified. 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.

Cystic Fibrosis

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.

For All Other Indications

For individuals who have other indications, (e.g., constitutional growth delay, counter the effects of aging/advanced age/symptoms of aging, anabolic therapy (except for AIDS), glucocorticoid-induced growth failure, short-stature due to Down's syndrome, intrauterine growth retardation, obesity, idiopathic dilated cardiomyopathy, juvenile idiopathic- or chronic-arthritis, or inflammatory bowel disease) who receive human GH, the evidence is lacking. Relevant outcomes include functional outcomes, QOL, and treatment-related morbidity and remain under investigation. 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. (110) The use of GnRH analogues was discussed as treatment options, but GH as a treatment option was not discussed.

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. (111) Evidence-based recommendations included the following:

- GHD is a well-recognized clinical syndrome in adults that is associated with significant comorbidities if untreated;
- GH should only be prescribed to patients with clinical features suggestive of adult GHD and biochemically proven evidence of adult GHD;
- No data are available to suggest that GH has beneficial effects in treating aging and age-related conditions and the enhancement of sporting performance; therefore, GH treatment

was not recommended for any reason other than the well-defined approved uses of the drug;
- No evidence exists to support any specific GH product over another.

American Gastroenterological Association

A 2022 American Gastroenterological Association clinical practice update on the management of short bowel syndrome notes that: "The use of recombinant human growth hormone has largely been discontinued due to unacceptable side effects and questionable long-term efficacy." (112)

Endocrine Society

In 2016, the Endocrine Society updated its practice guidelines on adult GHD included the following recommendation (113):

- 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 (114):

- 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 Paediatric Endocrinology Workshop (2008) published a consensus statement on the diagnosis and treatment of children with idiopathic short stature. (115) The statement indicated that the appropriate height below which GH treatment should be considered ranged from -2 to -3 standard deviation score. The optimal age for treatment was thought to be between 5 years and early puberty. The group noted that psychological issues should be considered (e.g., GH therapy should not be recommended for short children who are unconcerned about stature). The statement also mentioned that "psychological counseling is worthwhile to consider instead of or as an adjunct to hormone treatment."

The GHRS (2013) issued consensus guidelines on human GH therapy for Prader-Willi syndrome (PWS). (116) 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*. (117) 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 (118) 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.

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. (119) 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. (120) 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, the PES published guidelines for GH and insulin-like growth factor-1 treatment for children and adolescents with GHD, idiopathic short stature, and primary insulin-like growth factor-1 deficiency. (121) The guidelines used the GRADE approach (grading of recommendations, assessment, development, and evaluation). The following recommendations were made:

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

In 2017, the PES published practice guidelines on the management of Turner syndrome based on proceedings of the International Turner Syndrome Meeting. (122) The PES recommended initiating GH treatment early, around 4 to 6 years of age, and preferably before 12 to 13 years if the child had evidence of growth failure (<50th percentile height velocity) or had a strong likelihood of short stature (moderate quality of evidence).

National Institute of Health and Care Excellence

In 2013, the National Institute of Health and Care Excellence (NICE) issued guidance on human GH for growth failure in children. (123) 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.

Ongoing and Unpublished Clinical Trials

Currently ongoing or unpublished trials that might influence this policy are listed in Table 10.

Table 10. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05330325[a]	A Study Comparing the Effect and Safety of Once Weekly Dosing of Somapacitan With Daily Norditropin® as Well as Evaluating Long-term Safety of Somapacitan in a Basket Study Design in Children With Short Stature Either Born Small for Gestational Age or With Turner	399	Sept 2026

	Syndrome, Noonan Syndrome, or Idiopathic Short Stature		
NCT05171855[a]	A Multicenter, Open-Label, Extension Trial to Investigate Long Term Efficacy and Safety of Lonapegsomatropin in Adults With Growth Hormone Deficiency	240	Jan 2025
NCT01604395[a]	An Open, Multi-Center, Prospective and Retrospective Observational Study to Evaluate the Long-term Safety and Effectiveness of Growth Hormone (Eutropin Inj./Eutropin plus Inj.) Treatment with GHD, TS, CRF, SGA, ISS and PWS in Children	6000	Dec 2032
NCT04484051	Global Growth Hormone Study in Adults with Prader-Willi Syndrome	50	Oct 2026
NCT04615273[a]	foresiGHt: A Multicenter, Randomized, Parallel-arm, Placebo-controlled (Double-Blind) and Active-controlled (Open-label) Trial to Compare the Efficacy and Safety of Once-weekly Lonapegsomatropin With Placebo and a Daily Somatropin Product in Adults with Growth Hormone Deficiency	240	Dec 2024
Unpublished			
NCT00537914[a]	Long-term Phase IV Multicenter Study on the Safety and Efficacy of Omnitrope® (rhGH) in Short Children Born Small for Gestational Age (SGA)	278	Mar 2022 (completed)
NCT03038594	Growth Hormone Therapy for Muscle Regeneration in Severely Burned Patients	64	Nov 2021 (completed)
NCT01196156[a]	An Observational Phase IV Study for Prospective Follow-Up to Adult Height of a Cohort of Subjects Born Small for Gestational Age and Treated with Growth Hormone	443	Dec 2018 (completed)

CRF: chronic renal failure; GHD: growth hormone deficiency; ISS: idiopathic short stature; NCT: national clinical trial; PWS: Prader-Will Syndrome; rhGH: recombinant human growth hormone; SGA: Small for Gestational Age; TS: Turner Syndrome.

[a] Denotes industry-sponsored or cosponsored 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

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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.

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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**
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.