

## Human Growth Hormone

**Policy # 00188**

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

*Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.*

## When Services May Be Eligible for Coverage

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

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

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

### Patient Selection Criteria

The use of recombinant human growth hormone therapy may be considered **eligible for coverage\*\*** for any of the following indications:

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

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In addition to meeting the indication criteria:

- Patients must be prescribed Norditropin<sup>®</sup> and Genotropin<sup>®</sup> prior to other short-acting recombinant growth hormone (GH) products, including but not limited to Humatrope<sup>®</sup>, Nutropin<sup>®</sup>, Saizen<sup>®</sup>, Serostim<sup>®</sup>, Zomacton<sup>®</sup>, Zorbtive<sup>®</sup>, and Omnitrope<sup>®</sup>, unless there is clinical evidence or patient history that suggests the use of these products will be ineffective or cause an adverse reaction to the patient; OR  
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary \*\* if not met.)*
- Patients must be prescribed Skytrofa<sup>®</sup> and Sogroya<sup>®</sup> prior to other long-acting recombinant growth hormone (GH) products, including but not limited to Ngenla<sup>®</sup> unless there is clinical evidence or patient history that suggests the use of these products will be ineffective or cause an adverse reaction to the patient.  
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary \*\* if not met.)*

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

## When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of recombinant human growth hormone therapy for the following U. S. Food and Drug Administration (FDA)-approved indications or situations to be **not medically necessary**\*\*:

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

## When Services Are Considered Investigational

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

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

- Constitutional delay (lower than expected height percentiles compared with their target height percentiles and delayed skeletal maturation when growth velocities and rates of bone age advancement are normal)
- In conjunction with GnRH (gonadotropin releasing hormone) analogs as a treatment of precocious puberty
- Human growth hormone therapy in older adults without proven deficiency

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- Anabolic therapy except for acquired immune deficiency syndrome (AIDS) provided to counteract acute or chronic catabolic illness (e.g., surgery outcomes, trauma, cancer, chronic hemodialysis) producing catabolic (protein wasting) changes in both adult and pediatric patients
- 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
- Treatment of altered body habitus (e.g., buffalo hump) associated with antiviral therapy in human immunodeficiency virus (HIV)-infected patients
- Treatment of obesity
- Treatment of cystic fibrosis
- Treatment of idiopathic dilated cardiomyopathy
- Treatment of juvenile idiopathic or juvenile chronic arthritis
- Treatment of children with "genetic potential" (i.e., lower than expected height percentiles based on parents' height).

## When Services Are Not Covered

Based on review of available data, the Company considers the use of recombinant human growth hormone therapy EXCEPT for treating chronic renal insufficiency, AIDS wasting, Turner's Syndrome, Prader-Willi syndrome, Noonan Syndrome, wound healing in burn patients, growth delay in patients with severe burns, short bowel syndrome, short stature homeobox-containing gene (*SHOX*) deficiency, or growth hormone deficiency when a prescriber confirms the growth hormone deficiency with abnormal provocative stimulation testing to be **not covered**.\*\*

*Note: The use of recombinant human growth hormone is considered an exclusion in most member contracts except for the conditions listed as exceptions in the above section.*

## Policy Guidelines

The numbered guidelines correspond to the indications listed in the coverage section above.

### ***Medically Necessary Indications:***

1. Both children and adults (see Number 4, below) with proven GHD are considered appropriate candidates for GH therapy.

For adults, proven GHD is defined as:

- a. An abnormal response to TWO provocative stimulation tests, such as L-dopa, clonidine, glucagon, arginine, GH-releasing hormone (GHRH), or insulin. The insulin tolerance test is considered the best predictor of GHD; however, this test is contraindicated in patients with seizures or coronary artery disease. A provocation test using arginine and GHRH is also acceptable and is considered more stringent than tests using arginine alone or levodopa alone. Although an abnormal GH response has been traditionally defined as less than 10 ng/mL, different tests have different potencies, and the cutoff is likely to be lower when using monoclonal-based GH assays and rhGH reference preparations. Twenty-four hour continuous measurements

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of GH, serum levels of insulin-like growth factor (IGF-I), or serum of levels insulin-like growth factor-binding protein (IGFBP) are considered inadequate to document GHD.

- b. An abnormal response to ONE provocative stimulation test in patients with defined central nervous system pathology, history of irradiation, multiple pituitary hormone deficiency, or a genetic defect.
- c. Low IGF-I concentration in patients with complete hypopituitarism.

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

2. Chronic renal insufficiency is defined as a serum creatinine of greater than 1.5 mg/dL (or 1.4 for women and 1.7 for men) or a creatinine clearance  $\leq 75\text{mL/min per } 1.73\text{ m}^2$ . In patients with chronic renal failure undergoing transplantation, GH therapy is discontinued at the time of transplant or when the growth velocity is less than 2 cm per year, when epiphyseal fusion has occurred, or when the height reaches the 5<sup>th</sup> percentile of adult height.
3. AIDS wasting is defined as a greater than 10% of baseline weight loss that cannot be explained by a concurrent illness other than HIV infection. Patients treated with GH must simultaneously be treated with antiviral agents. Therapy is continued until this definition is no longer met.
4. Adults with GHD are defined as in No. 1 above. Only about 25% of those children with documented GHD will be found to have GHD as adults. Therefore, once adult height has been achieved, subjects should be retested for GHD to determine if continuing replacement therapy is necessary. These transition patients who require further treatment are usually started at doses of 0.4 to 0.8 mg/day, and titrated to maintenance doses of 1.2 to 2.0 mg/day. Adults with GHD not related to idiopathic deficiency of childhood (e.g., pituitary tumor, pituitary surgical damage, irradiation, trauma) are usually started at 0.1 to 0.3 mg/day; the dose is titrated to clinically desired end points (improved body composition, quality of life, reduction in cardiovascular risk factors), usually resulting in maintenance doses of 0.2 to 0.5 mg/day for men and 0.4 to 1.0 mg/day for women. The FDA cautions that the safety and effectiveness of GH therapy in adults aged 65 and over has not been evaluated in clinical studies. Therefore, it is noted that elderly patients may be more sensitive to the action of GH therapy and may be more prone to develop adverse reactions.
5. Turner's syndrome is defined as a 45, XO genotype.
6. Noonan Syndrome is a genetic disorder characterized by mildly unusual facial features, short stature, heart defects, bleeding problems, and skeletal malformations amongst other congenital abnormalities.
7. *SHOX* is a deficiency of short stature homeobox-containing gene causing short stature.
8. Prader-Willi syndrome is a genetic disorder characterized by a microdeletion in the long arm of chromosome 15. Clinically, the syndrome presents as a complex multisystem disorder characterized by excessive appetite, obesity, short stature, characteristic appearance, developmental disability, and significant behavioral dysfunction. Growth hormone deficiency has been demonstrated in most tested patients with Prader-Willi syndrome. Sleep studies are recommended prior to initiation of GH therapy for obese pediatric patients with Prader-Willi syndrome.

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

### ***Not Medically Necessary Indications:***

1. Pediatric patients born SGA. There are no established criteria for SGA or “catch-up” growth. However, in the data submitted to the FDA as part of the approval process, the mean height of enrolled patients was at least 2 standard deviations below the mean. Absence of catch-up growth was defined as a height velocity below 1 SDS, adjusted for age.
2. Pediatric patients with short stature. "Short stature" has been defined by the American Association of Clinical Endocrinologists and the Growth Hormone Research Society as height more than 2 standard deviations below the mean for age and sex. The FDA-approved indication is for children with a height SDS of -2.25 below the mean. Using this proposed definition, approximately 1.2% of all children would be defined as having idiopathic short stature and considered potentially treatable under these indications.

## **Background/Overview**

Human Growth Hormone (GH), also known as somatotropin, is synthesized in somatotrophic cells of the anterior lobe of the pituitary gland. GHD can occur due to a variety of conditions, such as:

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

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

Major points of controversy are what defines “inadequate secretion of normal endogenous growth hormone” and what constitutes “growth failure.” Before the availability of biosynthetic GH, GH was rationed to children with classic GHD, as defined by a subnormal response (<10 ng/mL, approximately, depending on GH assay) to GH provocation tests. However, the ready supply of GH

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has created interest in expanding its use to short-stature children without classic GHD, often referred to as partial GHD, neurosecretory GH dysfunction, constitutional delay in growth and development, or idiopathic short stature. “Classic” GHD is suggested when there is abnormal growth velocity (typically <10<sup>th</sup> percentile) or when height is more than 2 standard deviation scores below the current population mean, in conjunction with a chronologic age that is greater than the height age and bone age. Practically, interest in broadening the use of GH to non-GHD children has resulted in GH evaluation in many children who are simply below the third percentile in height, with or without an abnormal growth velocity.

These broadened patient selection criteria have remained controversial due to uncertainties in almost every step in the diagnosis and treatment process—selection of patients to be tested, limitations in laboratory testing for GH, establishment of diagnostic cutoffs for normal versus abnormal GH levels, availability of laboratory tests to predict response to GH therapy, changes in growth velocity due to GH therapy, whether resulting final height is significantly improved, and whether this improvement is clinically or emotionally significant for the patient. In addition, there are many ethical considerations regarding GH therapy, most prominently appropriate informed consent when the therapy is primarily requested by parents due to their particular psychosocial concerns about height.

In 2001, somatropin (Genotropin) received a U.S. Food and Drug Administration (FDA) labeled indication for treatment of pediatric patients born small for gestational age who failed to show catch-up growth by 2 years of age. Most children born small for gestational age normalize their stature during infancy, but about 15% maintain an exceptionally short stature at least throughout childhood. Epidemiologic surveys have suggested that the average adult height of men and women who did not exhibit catch-up growth as children is 5 feet, 6 inches, in men and 5 feet, 1 inch, in women. GH has been investigated in these children, based in part on the hypothesis that a GH resistance is a possible etiology of the growth retardation. In 2003, the FDA approved a recombinant 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.

The most common outcome measure reported in GH research is a change in height. For some situations, such as in patients with documented GHD or genetic disorder and short stature, improvements in height alone may be a sufficient outcome measure. However, in most situations, a change in height is not in itself sufficient to demonstrate that health outcomes are improved. There is insufficient evidence to establish that short stature is associated with substantial impairments in psychological functioning or quality of life, or that increases in height improve these parameters. Similarly, improvements in other measures of body composition (e.g., muscle mass, muscle strength) are not in themselves sufficient to establish that health outcomes are improved. Therefore, for most conditions in this evidence review, changes in other outcome measures, (e.g., functional status, quality of life, disease-specific clinical outcomes) are necessary to demonstrate an improvement in health outcomes.

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## **FDA or Other Governmental Regulatory Approval**

### **U.S. Food and Drug Administration (FDA)**

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

|                                                                             | Genotropin<br>(Pharmacia) | Humatrope<br>(Lilly) | Norditropin<br>(Novo-<br>Nordisk) | Nutropin<br>(Genentech) | Saizen<br>(Serono) | Serostim<br>(Serono) | Zomacron<br>(Ferring) | Zorbtive<br>(Serono) | Omnitrope<br>(Sandoz) | Sogroya<br>(Novo-<br>Nordisk) | Skytrofa<br>(Ascendis<br>Pharma) | Ngenla<br>(Pfizer) |
|-----------------------------------------------------------------------------|---------------------------|----------------------|-----------------------------------|-------------------------|--------------------|----------------------|-----------------------|----------------------|-----------------------|-------------------------------|----------------------------------|--------------------|
| Growth failure, peds<br>pts with inadequate<br>endogenous GH                | yes                       | yes                  | yes                               | yes                     | yes                |                      | yes                   |                      | yes                   | yes                           | yes                              | yes                |
| Growth failure due to<br>Prader-Willi<br>syndrome                           | yes                       |                      | yes                               |                         |                    |                      |                       |                      | yes                   |                               |                                  |                    |
| Replacement therapy<br>in adults with GHD                                   | yes                       | yes                  | yes                               | yes                     | yes                |                      | yes                   |                      | yes                   | yes                           |                                  |                    |
| Growth failure<br>associated with<br>chronic renal<br>insufficiency         |                           |                      |                                   | yes                     |                    |                      |                       |                      |                       |                               |                                  |                    |
| HIV wasting or<br>cachexia                                                  |                           |                      |                                   |                         |                    | yes                  |                       |                      |                       |                               |                                  |                    |
| Children born SGA,<br>who fail to show<br>catch-up growth by<br>age 2 years | yes                       | yes                  | yes                               |                         |                    |                      | yes                   |                      | yes                   |                               |                                  |                    |
| Short stature (height<br>SDS < -2.25) in non-<br>GH-deficient peds pts      | yes                       | yes                  | yes                               | yes                     |                    |                      | yes                   |                      | yes                   |                               |                                  |                    |
| Short stature due to<br>Turner's syndrome<br>(45, XO)                       | yes                       | yes                  | yes                               | yes                     |                    |                      | yes                   |                      | yes                   |                               |                                  |                    |
| Treatment of short<br>bowel syndrome                                        |                           |                      |                                   |                         |                    |                      |                       | yes                  |                       |                               |                                  |                    |
| Short stature in peds<br>pts with <i>SHOX</i><br>deficiency                 |                           | yes                  |                                   |                         |                    |                      | yes                   |                      |                       |                               |                                  |                    |
| Short stature in peds<br>pts with Noonan<br>syndrome                        |                           |                      | yes                               |                         |                    |                      |                       |                      |                       |                               |                                  |                    |

## **Rationale/Source**

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

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The evidence review was created in November 1997 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through August 18, 2023.

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical uses of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. 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.

### **Growth Hormone Deficiency**

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. Growth velocity improved compared with pretreatment values, and this improvement was maintained for at least 4 years. For children treated for at least 7 years, improvements in the mean height standard deviation score (SDS) ranged from 1.3 to 2.5, depending on the specific underlying condition. If treatment is started at an early age, most children can achieve a final height close to that expected from a parental height. In a study of 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.

Once-weekly lonapegsomatropin in children was compared to daily somatropin in children with GHD in an open-label randomized trial. 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. After 3 years of follow-up, the mean height SDS was similar between treatment groups.

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

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Meta-analyses of RCTs have shown evidence for increases in muscle strength and exercise capacity, although these findings were not robust across all studies. There is also evidence from meta-analyses that GH therapy is associated with increased bone mineral density (BMD) in adults with GHD. For example, a meta-analysis by Barakeet al (2014) identified 9 placebo-controlled randomized trials with at least 1-year follow-up on the effect of daily GH therapy on BMD. 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 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.

Ishii et al (2017) published an industry-funded, multicenter, observational study of GH therapy for adults with GHD. 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.

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

### **Short Stature Due to Prader-Willi Syndrome**

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

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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. 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. Sixteen RCTs and 20 non-randomized trials were included in the review; controls included placebo or no treatment. Among patients enrolled in RCTs, treatment with GH significantly improved height (1.67 SDS; 95% CI, 1.54 to 1.81 SDS;  $n=322$ ), body mass index z-scores (-0.67 SDS; 95% CI, -0.87 to -0.47 SDS;  $n=119$ ), fat mass proportion (-6.5% SDS; -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;  $n=114$ ) when compared to control. Data regarding cognitive function, behavior, motor development, and quality of life could not be pooled. However, improvements in cognition and motor development were demonstrated in small studies.

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. 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.

There have been numerous case reports of sudden unexpected death in patients with Prader-Willi syndrome undergoing GH therapy. 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.

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

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### **Short Stature Due to Chronic Renal Insufficiency**

Wu et al (2013) published a systematic review of RCTs evaluating the impact of GH therapy on height outcomes following a renal transplant in children 0 to 18 years of age. Five trials (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 MD in height SDS was 0.68 (95% CI, 0.25 to 1.11 SDS;  $p=0.002$ ) 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. To be included in the review, trials needed to include children 18 years of age or younger who were diagnosed with chronic kidney disease and were 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 <3<sup>rd</sup> percentile for chronologic age to <50<sup>th</sup> percentile for chronologic age). Overall, treatment with GH (28 IU/m<sup>2</sup>/week) compared with placebo or no specific therapy resulted in a statistically significant increase in height SDS at 1 year (8 studies; MD=0.82 SDS; 95% CI, 0.56 to 1.07 SDS). Moreover, a pooled analysis of 7 studies found a significant increase in height velocity at 1 year in the group receiving GH treatment compared with control (MD=3.88 cm/year; 95% CI, 3.32 to 4.44 cm/year).

An example of an individual RCT is Hokken-Koelega et al (1991), conducted in the Netherlands. 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<sup>2</sup>/day) 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. 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.

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

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### **Short Stature Due to Turner's Syndrome**

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. Eleven RCTs (N=1,122 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 MD [SMD], 1.22 cm; 95% CI, 0.88 to 1.56 cm;  $p<0.001$ ), and height velocity (MD=2.68 cm/year; 95% CI, 2.34 to 3.02 cm/year;  $p<0.001$ ) for patients receiving GH. After 1 year, bone age increased slightly for the GH group (standardized MD=0.32/year; 95% CI, 0.1 to 0.54/year;  $p=0.004$ ). 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 (N=365 patients) evaluating GH for treating Turner syndrome. Studies included children who had not yet achieved final height, received treatment for at least 6 months, and compared GH with placebo or no treatment. Only 1 trial reported final height, so outcomes could not be pooled. A pooled analysis of 2 trials reported that short-term growth velocity was greater in treated than in untreated children (MD=3 cm/year; 95% CI, 2 to 4 cm/year).

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. 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.

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

### **Short Stature Due to Noonan Syndrome**

Giacomozzi et al (2015) published a systematic review of literature on the effect of GH therapy on adult height. Included in the review were studies treating individuals with a diagnosis of Noonan syndrome with no other causes of short stature and a normal karyotype in females. In addition, studies had to follow patients for at least 3 years. Twenty-three studies were identified in a literature search conducted through April 2014, and 6 studies (N=177 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), 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 –

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1.4 (SD=0.9). Two uncontrolled studies reported near-adult height, which was -2.1 (SD=0.9). In addition, 2 studies reported a change in height SDS corresponding to 8.6 cm (SD=5.9). Mean gain in height SDS ranged from 0.6 to 1.4 cm by national standards, and between 0.6 and 2.0 cm by Noonan standards. The data were limited by the paucity of controlled studies and the lack of RCTs.

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

### **Short Stature Due to *SHOX* Deficiency**

A health technology assessment by Takeda et al (2010) assessed GH treatment of growth disorders in children and identified an RCT evaluating GH therapy for children with short stature due to *SHOX* deficiency. This industry-sponsored, open-label multicenter trial was published by Blum et al (2007). It included 52 prepubertal children at least 3 years of age who had *SHOX* deficiency. Height requirements were less than the third percentile of the local reference range or less than the 10<sup>th</sup> percentile with height velocity less than the 25<sup>th</sup> 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/year in the GH therapy group and 5.2 cm/year 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.

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). GeNeSIS was a prospective, multinational, open-label, pediatric surveillance program examining the long-term safety and efficacy of GH. The subset of the GeNeSIS population with *SHOX* deficiency consisted of 521 patients. Forty-nine of the 52 patients in the RCT enrolled in the long-term study. Patients in both studies will be followed until they achieve near-adult (final) height. Final height was defined as attaining 1 of the following criteria: height velocity less than 2 cm/year, 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%).

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%).

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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. 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 ( $p=0.030$ ) and growth velocity during the first year of therapy ( $p=0.008$ ).

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

### Severe Burns

A Cochrane review by Breederveld et al (2012) included RCTs evaluating the impact of GH therapy on the healing rates of burn wounds. 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 meta-analyses of studies that did not conduct survival analyses but did follow patients until their wounds healed. These analyses found significantly shorter healing time in patients who received GH therapy among adults (2 studies) and children (2 studies). A pooled analysis of 5 studies did not find a statistically significant difference in mortality among patients receiving GH therapy and placebo (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).

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

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. 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.

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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.

### **AIDS Wasting**

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

A double-blind RCT by Evans et al (2005) included 700 patients with HIV-associated wasting. 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.

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

### **Short Bowel Syndrome with Specialized Nutritional Support**

A Cochrane review by Wales et al (2010) identified 5 RCTs evaluating GH therapy for treating short bowel syndrome. Studies evaluated GH with or without glutamine treatment. The primary outcome was change in body weight. A pooled analysis of 3 small trials (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. However, the Cochrane review and the studies noted that the effects of increased intestinal absorption were limited to the treatment period. Specialized clinics may offer intestinal rehabilitation for patients with short bowel syndrome; GH may be a component of this therapy.

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 small RCTs found a significantly greater weight gain during GH therapy compared with placebo in patients with short bowel syndrome; other studies have found improved intestinal absorption during GH therapy in patients with short bowel syndrome receiving parenteral nutrition.

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### **Small for Gestational Age Children**

A meta-analysis of RCTs evaluating GH treatment for children born small for gestational age was published by Maiorana and Cianfarani (2009). Four trials (total N=391 children) 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/day 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 youth with short stature have either low self-esteem or a higher than average number of behavioral or emotional problems.

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. 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.

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 the psychological or functional outcomes associated with this additional gain in height.

### **Altered Body Habitus Related to Antiretroviral Therapy for HIV Infection**

Because high-dose GH has been associated with adverse events relating to inflammation, Lindboe et al (2016) conducted a randomized, double-blind, placebo-controlled trial to test the effect of low-dose GH in the treatment of HIV-infected patients on antiretroviral therapy. 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

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lowered C-reactive protein. Low-dose GH lowered soluble urokinase plasminogen activator receptors as well, but the difference was not statistically significant, even after controlling for age, weight, smoking status, and lipodystrophy.

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. The authors reported improved waist/hip ratio and mid-thigh circumference.

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. 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**

Several meta-analyses have assessed the impact of GH on idiopathic short stature and adult height. A Cochrane review by Bryant et al (2007) evaluated GH therapy for idiopathic short stature in children and adolescents. Ten RCTs met eligibility criteria; 3 studies were placebo-controlled, and the other 7 compared GH therapy with no treatment. Unlike the Deodati and Cianfarani (2011) review (described next), studies were not required to report final adult height. Nine of 10 studies in the Cochrane review were short term and reported intermediate outcomes. A pooled analysis of 3 studies reporting growth velocity at 1 year found a statistically significantly greater growth velocity in treated than in untreated children (Table 4). Five studies reported height SDS, but there was heterogeneity among studies, and findings were not pooled. These data would suggest that GH has an effect on height in children with idiopathic short stature in the short term but that evidence on GH's effects on adult height is limited.

Deodati and Cianfarani (2011) identified 3 RCTs and 7 non-RCTs. Adult height was defined as a growth rate of less than 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 a MD in height of more than 0.9 SDS (about 6 cm) to be a satisfactory response to GH therapy. Only 1 randomized trial was placebo-controlled, and that trial had a high dropout rate (40% in the treated group, 65% in the placebo group). Although GH treatment resulted in a statistically significant increase in adult height in the treated group, according to the a priori definition of a satisfactory response (difference, 0.9 SDS), the difference was not clinically significant. Moreover, there was a lack of high-quality, placebo-controlled randomized trials.

Paltoglou et al (2020) also evaluated the effect of GH therapy on linear growth and adult height in children with idiopathic short stature. 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. 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

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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."

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. These studies are briefly described next.

Shemesh-Iron et al (2019) published a 1-year blinded RCT and 3-year open-label study evaluating GH therapy in 60 prepubertal boys with idiopathic short stature (mean age, 10 years). 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) ( $p<0.001$  and  $p=0.022$ , respectively) and reduced short stature-related distress based on the Single-Category Implicit Association Test for height (SC-IAT-H;  $p<0.001$ ). After 4-years, GH therapy significantly improved scores on the Rosenberg Self-Esteem Scale (RSES) and SC-IAT-H ( $p<0.001$  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 idiopathic short stature without GHD. 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 CBCL and the Self-Perception Profile. No significant associations were found between attained height SDS or change in height SDS and annual changes in CBCL scores. There were no significant differences between groups on any CBCL summary scales in years 1 and 2, but, in year 4, there were significantly higher scores on the CBCL summary scales in the group receiving GH treatment. There were no significant differences between groups on the Self-Perception Profile at any follow-up point. This trial did not find a correlation between short stature and psychological adaptation or self-concept.

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

Downie et al (1996) examined the behavior of children without documented GHD who were treated with GH due to idiopathic short stature. Across measures of behavior, including IQ, self-esteem, self-perception, or parental perceptions of competence, there were no significant differences between

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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.

For individuals who have idiopathic short stature who receive human GH, the evidence includes RCTs and meta-analyses. Meta-analyses have found that GH treatment may increase height gain for children with idiopathic short stature but the difference in height gain may not be clinically significant. Many of the available studies did not follow treated patients long enough to determine the ultimate impact of GH on final adult height. 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.

### **Children With “Genetic Potential”**

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

For individuals who have “genetic potential” (i.e., lower than expected height percentiles based on parents’ height), no clinical trials evaluating GH therapy were identified. The evidence is insufficient to determine the effects of the technology on health outcomes. There is insufficient evidence to draw conclusions about the use of human GH to treat “genetic potential.”

### **Precocious Puberty**

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. 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, the difference in final height and targeted height, and height gain compared with those receiving GnRH alone (MD=2.8 cm [95% CI, 1.8 to 3.9 cm]; MD=3.9 cm [95% CI, 3.1 to 4.7 cm]; MD=3.5 cm [95% CI, 1.0 to 6.0 cm], respectively). When treatment duration was less than 1 year, no significant differences in the height outcomes were found.

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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. 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 analogs alone. The absence of final height data limited interpretation of this trial.

For individuals who have precocious puberty who receive human GH plus gonadotropin-releasing hormone, 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-analysis informing final height, the difference in final height and targeted height, and height gain. The meta-analysis reported statistically significant gains of several centimeters for patients who received the combination therapy for at least 1 year compared with patients receiving gonadotropin-releasing hormone alone. However, no studies have reported on the impact of short stature on functional or psychological outcomes in this population.

### **Older Adults with Age-Related Growth Hormone Deficiency**

A TEC Assessment (2001) investigated the use of GH in older adults with age-related GHD and concluded that there was insufficient evidence of efficacy. It is not possible to prove the effectiveness of GH treatment or lack thereof unless otherwise similar groups of treated versus nontreated patients are compared over a sufficient length of time to allow detection of any significantly and clinically different results.

For individuals who are older adults with age-related GHD who receive human GH, the evidence includes a systematic review (TEC Assessment). The TEC Assessment concluded there is a lack of evidence that GH therapy in older adults improves health outcomes. No subsequent controlled studies were identified.

### **Cystic Fibrosis**

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. Reviewers identified 4 RCTs (N=161 participants). All studies used daily subcutaneous injection of human GH as the intervention and included a no treatment or a placebo control group. All trials measured pulmonary function and nutritional status. Due to differences in how outcomes were measured, study findings were not pooled. Across trials, GH improved intermediate outcomes such as height and weight; however, improvements in lung function were inconsistent. No significant changes in QOL or clinical status were detected.

An update to the Cochrane review by Thaker et al was published in 2018. Eight trials (291 participants) were included in the revision, of which 7 compared standard-dose recombinant human growth hormone (rhGH; approximately 0.3 mg/kg/week) to no treatment, and a 3-arm trial (63 participants) compared placebo, standard-dose rhGH (0.3 mg/kg/week) and high-dose rhGH (0.5 mg/kg/week). Results showed that patients receiving rhGH demonstrated modest improvement in height, weight, and lean body mass between 6 and 12 months, but there was no consistent evidence that rhGH improved lung function, muscle strength, or QOL.

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Previously, a systematic review by Phung et al (2010) identified 10 controlled trials evaluating GH for treating patients with CF. One study was placebo-controlled, and 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).

An industry-sponsored, open-label RCT was published by Stalvey et al (2012). It compared GH therapy with no treatment in prepubertal children with CF younger than 14 years of age. Eligibility criteria included height less than the tenth 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/year in the treatment group and 5.3 cm/year 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 versus -1.9 at all 3 time points in the control group. The change in mean height SDS from baseline to 12 months was significantly greater in the treatment than in the control group ( $p < 0.001$ ). 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 1,209 liters at baseline, 1,434 liters at 12 months, and 1,467 liters at 18 months compared with 1,400 liters at baseline, 1,542 liters at 12 months, and 1,674 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.

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

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### **Policy History**

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

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|------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 10/29/2015 | Medical Policy Committee review                                                                                                                                                                                                                                                              |
| 11/16/2015 | Medical Policy Implementation Committee approval. Tev-Tropin is transitioning to the name Zomacton. Updated in the product chart. Updated background info sections.                                                                                                                          |
| 11/03/2016 | Medical Policy Committee review                                                                                                                                                                                                                                                              |
| 11/16/2016 | Medical Policy Implementation Committee approval. No change to coverage.                                                                                                                                                                                                                     |
| 01/01/2017 | Coding update: Removing ICD-9 Diagnosis Codes                                                                                                                                                                                                                                                |
| 09/07/2017 | Medical Policy Committee review                                                                                                                                                                                                                                                              |
| 09/20/2017 | Medical Policy Implementation Committee approval. No change to coverage.                                                                                                                                                                                                                     |
| 09/06/2018 | Medical Policy Committee review                                                                                                                                                                                                                                                              |
| 09/19/2018 | Medical Policy Implementation Committee approval. Updated FDA approved indication chart. No coverage changes.                                                                                                                                                                                |
| 11/07/2019 | Medical Policy Committee review                                                                                                                                                                                                                                                              |
| 11/13/2019 | Medical Policy Implementation Committee approval. No change to coverage.                                                                                                                                                                                                                     |
| 11/05/2020 | Medical Policy Committee review                                                                                                                                                                                                                                                              |
| 11/11/2020 | Medical Policy Implementation Committee approval. No change to coverage.                                                                                                                                                                                                                     |
| 09/02/2021 | Medical Policy Committee review                                                                                                                                                                                                                                                              |
| 09/08/2021 | Medical Policy Implementation Committee approval. Updated criteria to reflect that Norditropin must be prescribed before other growth hormone products. Updated background and rationale to match the most up to date information in the Association policy. Added a Not Covered Statement.  |
| 02/03/2022 | Medical Policy Committee review                                                                                                                                                                                                                                                              |
| 02/09/2022 | Medical Policy Implementation Committee approval. Added Sogroya and Skytrofa to the listing of available growth hormone products.                                                                                                                                                            |
| 02/02/2023 | Medical Policy Committee review                                                                                                                                                                                                                                                              |
| 02/08/2023 | Medical Policy Implementation Committee approval. No changes to coverage eligibility. Updated with literature review through August 2022.                                                                                                                                                    |
| 05/04/2023 | Medical Policy Committee review                                                                                                                                                                                                                                                              |
| 05/10/2023 | Medical Policy Implementation Committee approval. Updated criteria to reflect that Norditropin and Genotropin must be prescribed before other growth hormone products.                                                                                                                       |
| 04/04/2024 | Medical Policy Committee review                                                                                                                                                                                                                                                              |
| 04/10/2024 | Medical Policy Implementation Committee approval. Added Ngenla to the listing of available growth hormone products. Updated literature review through August 2023.                                                                                                                           |
| 06/06/2024 | Medical Policy Committee review                                                                                                                                                                                                                                                              |
| 06/12/2024 | Medical Policy Implementation Committee approval. Updated criteria to reflect that Skytrofa and Sogroya must be prescribed before other long acting growth hormone products. Also clarified Norditropin and Genotropin must be prescribed before other short acting growth hormone products. |
| 08/07/2025 | Medical Policy Committee review                                                                                                                                                                                                                                                              |
| 08/13/2025 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged.                                                                                                                                                                                                            |
| 08/12/2026 | Pre Pharmacy & Therapeutics Committee review.                                                                                                                                                                                                                                                |
| 08/19/2026 | Pharmacy & Therapeutics Committee approval. Coverage eligibility unchanged.                                                                                                                                                                                                                  |

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## **Coding**

*The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2025 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.*

*The responsibility for the content of Louisiana Blue Medical Policy Coverage Guidelines is with Louisiana Blue and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Louisiana Blue Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Louisiana Blue Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.*

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

| Code Type        | Code                       |
|------------------|----------------------------|
| CPT              | No codes                   |
| HCPCS            | C9399, J2941, J3590, S9558 |
| ICD-10 Diagnosis | All related diagnoses      |

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

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

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

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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

‡ Indicated trademarks are the registered trademarks of their respective owners.

**NOTICE:** If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

**NOTICE:** Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

**NOTICE:** If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan’s authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan’s pharmacy benefit.