

A collage of 12 diamond-shaped photographs arranged in a grid. The photos feature various individuals: a woman and a young girl, a group of four adults, a young boy in a blue shirt, a man with glasses and a pink shirt holding a small black dog, a young boy in a red shirt, a young girl with glasses, a woman holding a young girl, a young boy in a light blue shirt, a young girl in a colorful dress, a young boy in a blue shirt, and a woman in a blue shirt. The background is decorated with colorful geometric shapes like triangles and diamonds in shades of purple, green, and blue.

Revised by the Clinical and Scientific Advisory Board of PWSA | USA with special thanks to Barbara Y. Whitman, Lynn Garrick, Moris Angulo, and Karen Vogt



GROWTH HORMONE AND PRADER-WILLI SYNDROME THIRD EDITION

***A Reference for Families
and Care Providers***

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About This Publication

DEDICATION - This publication is dedicated to the committed people whose efforts have brought us to this point of knowledge about growth hormone treatment — the research scientists who conducted growth hormone studies, the children and adults with PWS and their families who willingly participated, and all who advocated for acceptance of this new treatment to improve the lives of people with Prader-Willi syndrome.

EDITOR'S NOTE - While the information in this booklet is believed to be accurate at the time of publication, it is not intended to be a substitute for medical advice, which should be obtained from qualified professionals.

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1. Introduction and History

Since 2000, the use of growth hormone (GH) has become the standard of care for individuals with Prader-Willi syndrome (PWS) when prescribed by an experienced endocrinologist. In infants and children with PWS, recombinant human GH (rhGH) can help with height, weight, body mass, strength and agility, and also may help with attention and cognitive development. In addition, studies of the use of human GH in adults with PWS have shown positive results in the areas of bone strengthening, improved body composition including improved lean muscle mass, greater energy and endurance, and modest improvements in cognition.

Prior to 1990, although there were several case reports, there were no controlled studies of the use of human GH in individuals with Prader-Willi syndrome.

At that time, there was considerable debate among researchers about whether children with PWS have a true growth hormone deficiency (GHD). This was an important question because GH treatment had only been approved for children with GHD and a few other rare conditions. While some children with PWS did get treatment, others were denied treatment because it could not be proven that they had evidence of growth hormone deficiency through provocative testing. Even if a doctor prescribed GH, the family's health insurance plan might refuse to cover the cost because it was considered an "experimental" treatment in children with PWS. Subsequent studies of children with Prader-Willi syndrome confirm that PWS causes a true disorder of GH secretion, resulting in absolute or functional growth hormone deficiency.

Pioneering some of the earliest reported work in this area were Dr. Moris Angulo, who serves on the Clinical and Scientific Advisory Board of PWSA | USA, and Dr. Phillip Lee then of Baylor College of Medicine in Texas, a past member of the Scientific Advisory Board of PWSA | USA. Dr. Lee, who reported on the use of GH with a handful of patients in 1987 at a PWS meeting in Houston, is also credited with organizing the first PWS GH symposium, held at the 1999 PWSA | USA conference in San Diego. Subsequently Dr. Angulo made a presentation in Jerusalem, Israel in October 1989 documenting GH deficiency in five children with PWS.

Reports of the first "controlled" studies of GH therapy in individuals with Prader-Willi syndrome began to appear in medical journals in the 1990s. Dr. Moris Angulo in 1996 published "Growth Hormone Secretion and Effects of Growth Hormone Therapy on Growth Velocity and Weight Gain in Children with Prader-Willi Syndrome." Dr. Martin Ritzen from Sweden reported at the 1998 national conference of PWSA | USA results from a major study to compare children with PWS treated with growth hormone therapy to a similar group of children who were not treated. His results indicated that not only did GH treatment increase height and growth rate dramatically, it also increased muscle mass, improved bone development and modestly reduced body fat. This was followed in 1999 by reports of a USA study of growth hormone deficient children with PWS by Myers, Carrell, Whitman et al, who showed equally dramatic results. An international consensus statement signed by 21 endocrinologists worldwide was initially published in July 2000, stating that "GH testing and treatment should be made available to all children with PWS" and that "consideration should be given to eliminating the need of GH stimulation testing before treatment."

A second, even stronger international consensus statement providing guidelines for recombinant growth hormone therapy in Prader-Willi syndrome was published in 2013.

Immediately prior to the July 2000 consensus statement publication, the U.S. Food and Drug Administration (FDA) took action. In June 2000, the FDA approved an application from Pharmacia Corporation (since acquired by Pfizer), the makers of the Genotropin® brand of recombinant growth hormone, to market and promote its product for the treatment of growth failure due to Prader-Willi syndrome. For families in the United States, this FDA decision removed one of the last barriers to obtaining growth hormone for their children. Because Prader-Willi syndrome is an approved “indication” for GH medication, children with PWS in this country can now be considered for GH treatment based solely on their genetic diagnosis and growth pattern, rather than on the results of GH stimulation testing.

Although human GH treatments do not decrease appetite, these therapies — together with early intervention, and in conjunction with dietary, environmental and lifestyle interventions — have helped to create a whole new generation of children with PWS who are taller, slimmer, more active and alert, and who are living much longer and healthier lives. This publication is intended to help both families and care providers understand the issues involved so that they, together with their endocrinologist, can make decisions in the best interests of their child or adult with PWS.

2. Prader-Willi Syndrome and Growth

A Different Pattern of Growth

Children with Prader-Willi syndrome (PWS) grow and develop in ways that are different from other children. Two primary reasons for the atypical pattern of growth seen in children with PWS are 1) a skewed body composition from birth and 2) for most children with PWS, an insufficient production of certain hormones needed for normal growth. While there are individual variations, the following history is common for children with PWS who do not receive growth hormone treatment.

Infancy and early childhood — While most children with PWS are born with normal weight and length, statistics show that approximately 30 percent of these infants are born with low birth weights. Most newborns with PWS are described as “floppy infants” because of their low muscle tone (hypotonia). Because of the low muscle tone, most infants with PWS have trouble feeding and gaining weight. Most require special feeding techniques in order to survive and grow. With gradual improvements in strength and muscle tone, these youngsters begin to reach their major motor milestones (sitting up, walking, etc.), although usually later than other children.

As young children with PWS continue to develop, their body fat seems to grow at a greater rate than their muscle and height. Height measurements taken on a number of children with PWS show that at least half are growing at a rate far below average as early as age 2 and that most end up below the 5th percentile after adolescence. Although eating well, many continue to be weaker and less active than other children. The toddler or preschool child with PWS often begins to desire more food than his or her young body can use, and excess weight can build quickly.

In April 2011, a group of 10 U.S. researchers published standardized growth curves for infant boys and girls with PWS ages 0-36 months and “naïve” to growth hormone. Included in the five sets of growth curves, representing 108 boys and 78 girls, are data analyzed for weight, length, head circumference, weight/length and body mass index (BMI). All information was compared to the 50th percentile national growth data for non-affected children released in 2003 by the Centers for Disease Control and Prevention. In developing the PWS specific growth curves, the researchers reported that “no significant differences in growth measurement were seen when comparing the data among infants (boys or girls) with PWS having the 15q11-q13 deletion or other genetic defects, including maternal disomy 15.” The authors note: We encourage the use of these growth standards (by the clinician and dietitian) when examining infants with PWS and evaluating growth for comparison purposes, monitoring for growth patterns, nutritional assessments, and recording responses to growth hormone therapy commonly used in infants and children with PWS.”

Similar curves for youngsters naïve to growth hormone treatment ages 3-18 years were published in 2015. These standardized curves were supplemented with a set of curves for youngsters with PWS treated with growth hormone ages birth to 18 were published in 2016.

These data were published in *Pediatrics*, the official journal of the American Academy of Pediatrics, and are reprinted with permission on pages **47-51** of this publication.

Infancy and early childhood — Through the school-age years, a typical physical profile usually becomes apparent in the child with PWS who has not received the benefits of human growth hormone therapy. Recall that we have previously indicated that height measurements of many children with PWS show that at least half are growing at a rate far below average as early as age 2 and that most end up below the 5th percentile after adolescence. As a result, he or she is likely to be short in stature (compared with that of classmates and other family members); has small hands and feet; and has poor muscle development with excess fat, especially in the middle of the body. Studies of body composition have found that children and adults with PWS tend to have more than twice the amount of body fat as others their age — often measuring around 40 to 50 percent of their total body weight.

At the usual time of puberty, the differences between youngsters with PWS and their peers become even more obvious. Without growth hormone treatment, teens with PWS do not experience the typical adolescent growth spurt and most do not develop the body changes associated with sexual development. Thus, most adults with PWS are shorter than nearly all other adults. (*See height charts on page 52*)

Note: These are not the only characteristics of Prader-Willi syndrome. For a more complete overview of PWS, see Appendix A.

What Causes These Growth Problems?

To understand growth and growth hormone treatment in Prader-Willi syndrome, it is helpful to have a basic understanding of how the hormone — or endocrine — system normally works. The endocrine system is made up of all the glands that produce and release hormones into the bloodstream.

Researchers strongly suspect that one member of the endocrine system, the hypothalamus is the main source of the growth differences in PWS. A tiny part of the central brain, the hypothalamus connects the body's two key systems for survival and maintenance — the nervous system and the endocrine system. In addition to playing a key role in growth and sexual development, the hypothalamus also contributes to the regulation of appetite, metabolism, body temperature, and mood. These are functions that we know are affected in people with PWS.

Just below the hypothalamus, and directly attached to it, is the pituitary gland. Called the “master gland” because it receives messages from the hypothalamus and relays them to the other endocrine glands, the pituitary gland also makes and releases many hormones. Among these are growth hormone (GH), gonadotropins (LH and FSH) to stimulate the gonads (Testis and ovaries) to produce sex hormones for sexual development and reproduction, TSH to stimulate thyroid gland and ACTH to stimulate to produce the stress hormone, known as cortisol.

How Growth Hormone Works

When functioning properly, the growth hormone process begins when the hypothalamus sends a chemical messenger called growth hormone releasing hormone (GHRH) to the pituitary gland. This

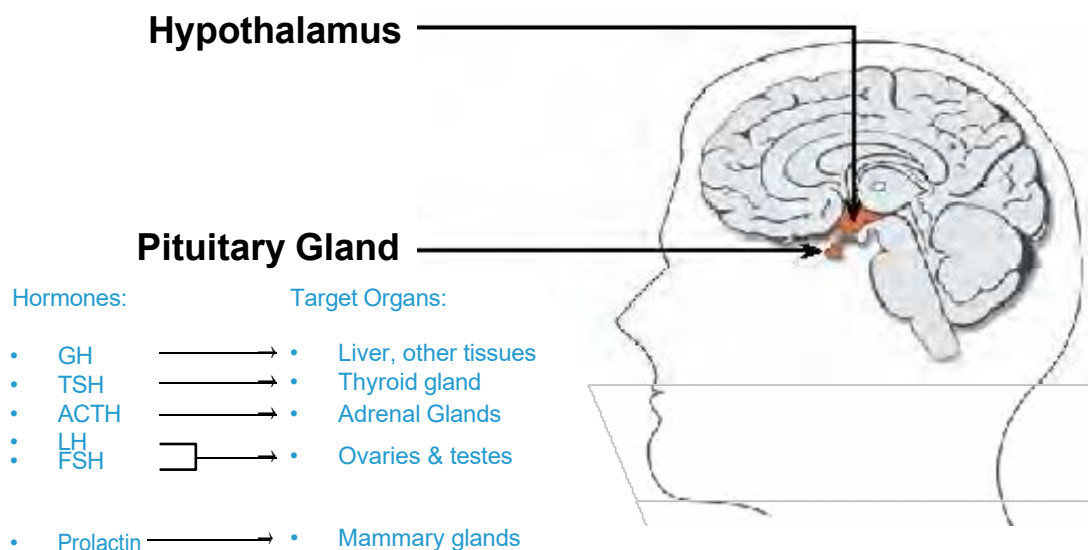
signals the pituitary to release growth hormone, which it does in small spurts throughout the day, but especially during the first hours of sleep.

GH travels throughout the bloodstream to target cells with GH receptors that are programmed to respond. There are GH receptors in many organs in the body, but the most important of these is the liver. Growth hormone does not directly cause most of the growth in bones and body tissue, rather it signals the liver to make and release the substances that do — the insulin-like growth factors (IGF). The main one of these is a protein called insulin-like growth factor-I (one), or IGF-I (responsible for about 80% of growth and anabolic promoting effects). It is IGF-1 that stimulates new cell growth in the cartilage near the ends of the skeletal bones (called the epiphyses) and in the muscle tissues, therefore this protein is commonly used to monitor GH's dose while on GH treatment.

The body's growth system also has checks and balances. For example, when there is a high level of GH or IGF-I in the system, the hypothalamus receives a message and then produces a different hormone called somatostatin, which tells the pituitary gland to stop releasing GH into the bloodstream.

Growth Problems and Treatment

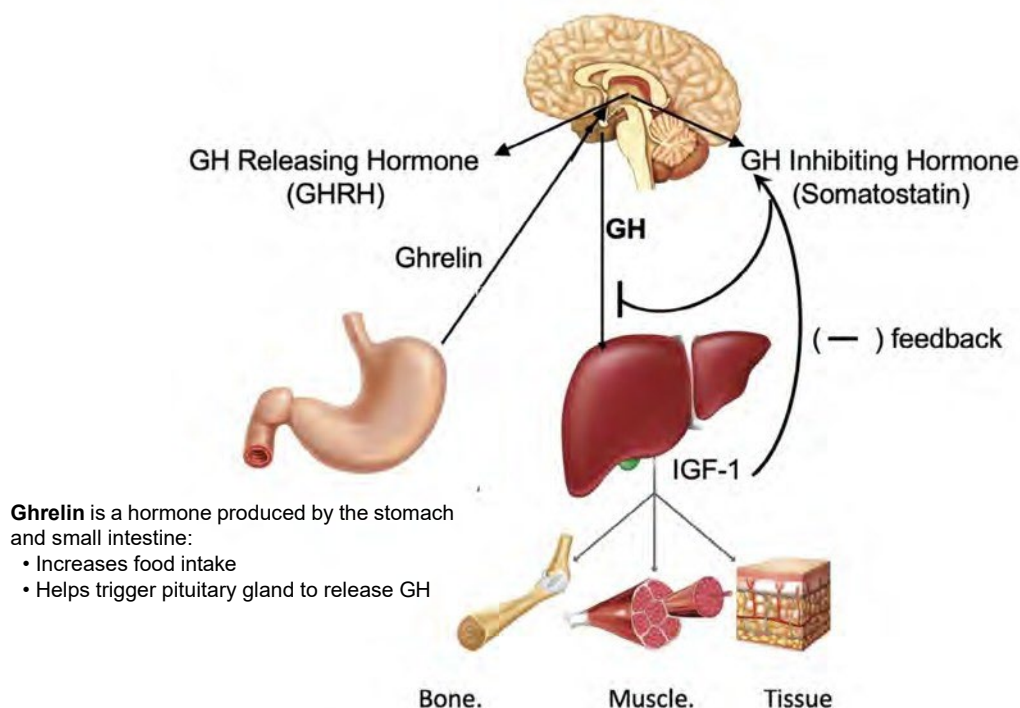
Growth can be adversely affected if there is a problem in any part of the system: the hypothalamus, the pituitary gland, the liver or the feedback system to the hypothalamus. It is likely that the function of one or more of the missing genes responsible for causing PWS results in failure to supply essential instructions to the hypothalamus and thus the hypothalamus fails to relay hormone production instructions to the pituitary gland or to receive messages from the liver. If the pituitary gland does not make or release enough required hormones, or makes hormones that are not effective in the body, then the other glands and organs that depend on them cannot do their jobs.



Growth hormone (GH) is one of six major hormones produced and stored in the front (anterior) lobe of the pituitary gland. Pituitary hormones are released into the bloodstream and travel to their target organs, where they stimulate additional action or hormone release.

The Growth Hormone/IGF axis consists of IGF-1, and several high and low affinity IGF Binding Proteins (IGFBPs). The whole system is tightly regulated by a feedback loop involving Growth Hormone (GH) secreted by the pituitary, and GH production and secretion controlled by Growth Hormone Releasing Hormone (GHRH) at the hypothalamus.

As previously indicated, GH is produced by our master gland (Pituitary gland). Most (80%) of its effects is through another protein, Insulin-like growth factor (IGF-1) synthesized by the liver. Other factors such as Ghrelin from the stomach may also stimulate GH release. As you can see in the figure, GH has not only growth promoting and an anabolic effect on bone and muscle, it also stimulates the breakdown of fat.



When there is a disruption in the system, signs of growth hormone deficiency may begin to appear, including many of the growth-related characteristics seen in people with PWS such as slow growth rate, short stature, insufficient muscle growth and development, increased central body fat, and reduced activity level.

Growth also is affected by other parts of the endocrine system, such as the thyroid and reproductive hormones (both of which are often insufficient in individuals with PWS), as well as by an individual's diet, sleep, and exercise level. Fortunately, scientists have learned that it is possible to replace or supplement growth hormone when the body does not produce enough.

Growth hormone treatment is the addition of recombinant human growth hormone (rhGH) to the body to make up for what the pituitary gland fails to produce. GH must be given as an injection because it is a protein hormone that would be destroyed by digestion if taken in pill form.

Giving growth hormone treatment to someone who needs it is no different than giving insulin to a person with diabetes or thyroid hormone to someone with thyroid deficiency.

The Need for Growth Hormone Treatment in PWS

Clinical trials of GH in children with PWS clearly demonstrate that many of the growth-related problems outlined at the start of this section can be corrected, at least partially, if GH treatment is started early enough. It has also been demonstrated that adults with PWS, even those who never had GH treatment as children can benefit from GH therapy.

Sections 3, 4, and 5 of this publication will discuss in greater detail the benefits and risks of using GH, as well as some of the vital information needed before starting GH treatment as an infant, child, or adult with PWS.

3. EFFECTS OF GROWTH HORMONE TREATMENT IN CHILDREN WITH PRADER-WILLI SYNDROME

Reports from research groups around the world confirm what was suspected in the late 1980s: growth hormone treatment (GHT) offers many benefits to children and adults with Prader-Willi syndrome (PWS). Some questions remain: How young do you start GHT? Is there an age when you stop GHT? Information in this section addresses the benefits and potential side effects of GHT.

Benefits of GH treatment

Measured Improvements

The following positive physical changes have been documented in various research studies. It must be remembered that the first studies were conducted on children ages four to thirteen years. For those children, dramatic “catch-up” growth was observed, particularly in the first year of treatment and particularly in the hands, feet, and facial features. Most children today initiate treatment as infants, so that the improvements listed below will be more subtle and evolve continuously over time.

- **Increased height and growth rate** — Treated children grow in height at double or more the rate they were growing before treatment. For example, some study participants grew five or more inches during the first year of treatment, compared with two inches a year or less prior to GH treatment. A child treated with GH measures higher on the normal growth curves than before treatment and continues to grow along that higher curve as long as GH therapy is continued. Depending on the age of starting treatment, a child’s final height can be closer to that of children in the general population without PWS. Both standard and PWS specific growth and weight charts should be used to compare with general population while on GH treatment.
- **Improved respiratory function** — GH-treated children can breathe better, due to stronger respiratory muscles and improved response to build-up of carbon dioxide (CO₂). This is particularly evident in infants and toddlers.
- **Increase in resting energy expenditure (REE)** — At least one study records an improvement in REE after two years of treatment. REE is the level of calories a body burns while at rest, which is most of the day’s calorie usage, or the individual’s basic rate of metabolism. REE is raised by adding muscle and increasing physical activity.
- **Increase of hand and foot sizes to normal proportions** — GH treatment enables hand and foot sizes to catch up with height growth, often in just one year. Without GH treatment, individuals with PWS typically have smaller hands and feet than would be expected for their body size, which can affect motor skills.
- **Increase in muscle amount (termed mass) and development** — Improvements have been shown in measured size of muscles, in muscle as a percent of body weight, and in muscle tone. While the amount of muscle does not fully reach normal levels, it is significantly improved. Young, underweight children in one study gained weight because of the increased

muscle. The benefits of increased muscle mass and strength are increased activity and improved metabolism. While these improvements are crucial at any age, when GH is started in infancy, improved muscle development may contribute to earlier achievement of motor milestones and to the capacity of the developing infant to explore their world. Such exploration may contribute to improved early cognitive and social development.

- **Improved physical performance** — Studies document improvements in physical performance with GH treatment due to increased muscle strength and respiratory function. Children are able to run faster, jump farther, lift more weight and do more sit-ups than those who were not treated with GH.
- **Increase in bone mineral density (BMD)** — Researchers have found that BMD increased at a faster rate in children who were treated with GH for one year than in those who were not treated. Continued increases after two years of treatment suggest that GH therapy may help to avoid osteoporosis (thinning of the bones), which is a concern for adults with PWS.
- **Improved head circumference** — Several studies of children with PWS who received growth hormone treatments from infancy for a period of six years show a much more normal head circumference. This result may serve as an index for better brain growth.
- **Improved cognition** — Some studies suggest that prompt initiation of GH treatment in infancy may facilitate the development of cognition at the same rate as their unaffected peers. And comparison studies of affected individuals treated since infancy into early childhood do seem to show better scores on cognitive tests. Many studies do report improved attention in youngsters treated with growth hormone, which may in part account for improved cognitive test scores, nonetheless long term studies are necessary to document that improved cognition is stable and is not a function of the test demands for younger children that do not rely as much on verbal skills and abstract thinking.
- **Decrease in body mass index (BMI)** — BMI, which is a measurement of obesity based on weight and height, declines with GH treatment, and increases when treatment is stopped.
- **Improvement in cholesterol levels** — Studies show that total cholesterol decreases in treated children, while their HDL (high-density lipoprotein, or so-called “good cholesterol”) levels rise.
- **More typical body fat accumulation during growth** — Excess fat tissue is a characteristic of PWS. GH treatment, particularly when initiated in infancy, appears to modify the total amount of excess fat tissue. However, in most treated individuals the amount of fat tissue remains increased when compared to age-matched peers without Prader-Willi syndrome.

Parent Observations

Parent reports collected during several of the studies suggest that GH treatment may bring a number of real-life benefits for children with PWS and their families:

- ***Improvement in alertness and activity level***
Treated children seem to have more energy and stamina for daily activities.
- ***Improvement in motor skills and athletics***
Parents seemed most impressed by their children's new muscle strength and abilities. Some reported that their children were able to try new sports or other physical activities; others reported better strength and independence in everyday tasks, such as climbing bus steps and carrying groceries.
- ***Subtle behavior improvements***
A behavior survey conducted periodically as part of a U.S. growth hormone study suggests that GH treatment may have positive effects on depression, obsessive-compulsive or repetitive type behaviors and skin-picking in children with PWS.
- ***Improved size and appearance***
It is obvious from the photos throughout this publication that children treated with GH begin to look more like other children their age. In addition to fostering better self-esteem, parents note practical benefits, such as being able to buy clothing off the rack to fit their children.
- ***Improved family relations***
Many families report that sibling relationships improve when their affected sibling no longer "looks different".
- ***Variable effects on behavior issues and temper outbursts***
Because behavior is such a concern in PWS, an early U.S. research study on GH specifically surveyed parents on behavior before and throughout the GH treatment period. Neither this nor any other study found an increase in problem behaviors because of GH treatment, but one report noted that behavior seemed to become worse when treatment was stopped. Families of physically aggressive children may have cause for concern about their child gaining size and strength with GH treatment. These families are advised to seek help from a behavior specialist, whether or not their child begins GH treatment.

Areas of No Change

None of the studies on GH treatment in children with PWS has documented either an improvement or a worsening in any of the following:

- ***Appetite and food-seeking behaviors***
Although some parents have reported that their child's appetite either increased or decreased while on GH treatment, none of the studies of children with PWS documented a change in appetite and food-seeking behaviors. Even for the children on GH who could eat extra calories, diet restrictions remained necessary.

- ***Bone age (used as a predictor for when a child stops growing)***

GH treatment does not appear to speed up bone age advancement. (If bone age advances too quickly, the period of growth potential becomes shorter.) Many children with PWS have delayed bone age, which is associated with growth hormone deficiency. Increased peripheral androgen aromatization.

What happens if my child stops GH treatment?

People who stop taking growth hormone will probably see their growth slowing down, but they will gradually lose the other physical benefits that GH produces, i.e., muscle development, fat reduction, increased energy level, and will most likely gain weight. If your child is benefiting from GH therapy but needs to stop because of a side effect, it may be possible for him or her to continue treatment at a lower dosage level, or to stop treatments and then restart them after the problems are understood and addressed. Even a low dose can improve body composition. There is generally no problem with stopping and restarting GH treatment, but risks and benefits of treatment should be discussed with your doctor.

Side Effects

As with any medication, GH therapy may have undesirable side effects in some cases. Therefore, the risks and benefits of GH treatment should be thoroughly discussed with the individual's physicians prior to initiating treatment.

The most common side effects are minor, such as changes in the skin at the injection site, e.g., occasional bruising, slight bleeding, tiny bumps on the skin, or an indentation at the injection site (from overuse of that site or a particular injection method). Some of these effects can be avoided or corrected with a change in injection procedures or devices. Although collectively studies of individuals with PWS report no widespread side effects of GH treatment, there are rare reactions that do sometimes occur:

- **Headaches**

Some individuals get headaches during GH treatment, probably due to the pressure of extra fluid in the body. This symptom usually occurs within the first eight weeks of treatment. While the headaches sometimes stop on their own, in some cases it may be necessary to lower the dosage and gradually increase the growth hormone dose. Rarely, more frequent or intense headaches may develop that also may be accompanied by vomiting and vision disturbances due to fluid pressure in the brain.

This condition, called intracranial hypertension or pseudotumor cerebri is commonly suspected by papilledema (swelling of the optic discs in both eyes), and diagnosed by ophthalmologists as well as endocrinologists. When this occurs, the affected person should contact their physician immediately. Although the symptoms are very serious, they go away when GH treatment is stopped. The individual often is able to restart GH at a lower dose and work up gradually to the higher dose without this problem recurring.

- **Swelling in the feet and legs (edema)**

Edema, due to fluid build-up, has been reported in a few cases during the beginning of treatment. This is more common in the adult population with PWS (up to 40%). This problem may go away on its own, or the GH dose may need to be decreased in order to resolve it.

- **Increased levels of insulin**

Low levels of insulin are found in children with PWS before GH treatment, and those levels can rise significantly during treatment. Insulin is a hormone produced by the pancreas that is required for carbohydrate and glucose metabolism. Although the increased insulin usually stays within normal levels, cases have been reported in which a GH-treated child became resistant to insulin and developed Type 2 diabetes. In each case, this occurred after significant weight gain (obesity interferes with the body's insulin receptors), and the diabetes disappeared when GH treatment was stopped and insulin levels decreased. Individuals with PWS and GH deficiency should be monitored carefully for signs and symptoms of glucose intolerance during GH treatment, particularly if they are morbidly obese or have a family history of diabetes mellitus.

- **Decreased levels of thyroid hormone (thyroxine)**

Some individuals with PWS develop thyroid deficiency after starting GH treatment and require monitoring thyroid hormone levels including TSH, T4 and Free T4 before considering oral thyroid hormone replacement.

- **Respiratory dysfunction**

A careful history and assessment of respiratory abnormalities should be evaluated prior to and during GH therapies. **Individuals with sleep apnea** should be evaluated by a pulmonologist and sleep medicine specialist, otolaryngologist, and gastroenterologist before and shortly after beginning GH treatments. (Please See Appendix I — Recommendations for Evaluation of Breathing Abnormalities Associated with Sleep in PWS.)

- **Progression of scoliosis (curvature of the spine)**

Children with PWS have about a 70% risk for developing spinal curves including scoliosis and kyphosis, probably because of weak muscles and loose joints. Although rapid growth can cause a scoliosis curve to worsen, studies found no significant difference in curve progression between individuals with scoliosis who were treated with GH and those not receiving GH treatment. It appears that the overall benefits of GH for the child with PWS greatly outweigh any effect of the GH on spinal curves. In general, spine curves may need treatment such as bracing or surgery. GH is known to improve bone mineral density which can be very important to the success of a surgical procedure for severe scoliosis. Decisions to initiate or continue GH treatments in an individual with spinal curvature abnormalities should be made in consultation with an endocrinologist and an orthopedic surgeon experienced in PWS.

- **Elongation of lower face**

Also described as a “high mid-face,” this subtle change in proportion of the face after GH treatment has been noted by several PWS researchers. The lower jaw tends to be more responsive to GH treatment than the upper jaw, which may account for these facial changes. There is no appearance of deformity from this change in the jaw, but it may affect teeth alignment and plans for orthodontic treatment (braces).

- **Acromegaly**

This is the term for extreme overgrowth of the hands, feet, or face caused by too much growth hormone in the body, a rare condition usually caused by a tumor on the pituitary gland. Acromegaly features are the risk for anyone who receives an excessively high dose of GH over a period of time. It is particularly important to avoid giving dosages meant for a growing child to a teen or adult whose growth plates have closed. Periodic bone age x-rays are usually done to guard against this possibility.

STANDARD WARNINGS

The patient literature about growth hormone discusses several other possible side effects of GH treatment. None of the following have been reported in any PWS research studies; the most serious of these are considered to be extremely rare.

Arthralgia, myalgia, carpal tunnel syndrome — Various types of joint and muscle pain have been reported with GH use, more commonly in adults with GH deficiency who experience them at the beginning of treatment. Usually, such pain disappears within a few months.

Tumor/cancer spread — When growth is stimulated, abnormal and malignant growths may also respond. If an individual has an active tumor or cancer, growth hormone therapy is not advisable.

An individual who has had cancer but has been in remission for a period of time might still be considered for treatment. The risks and benefits need to be thoroughly discussed with the involved physicians.

Slipped-capital femoral epiphysis (SCFE) — This term describes a condition almost like a break in the top of the thigh bone (femur). There is a fracture, or slippage, through the growth plate (or the epiphyseal plate) at the top of the thigh bone (femur) for reasons not well understood and causes a hip deformity. This injury has occurred very rarely with GH treatment, and obesity seems to put an individual at greater risk. Symptoms of the problem include hip pain and stiffness, knee pain and limping. Since this injury requires surgical correction, an orthopedic surgeon should be consulted if these complaints arise.

4. WHAT IS INVOLVED IN GROWTH HORMONE TREATMENT?

This section provides a question-and-answer look at some of the key aspects of GH treatment beginning in childhood. Additional information on growth hormone and treatment considerations is available from a number of sources listed in Appendix C.

Who determines the need for GH treatment?

All individuals with PWS need a primary care physician. However, an endocrinologist is required when deciding whether a child or adult can be treated with growth hormone. Both pediatric and adult endocrinologists are doctors who specialize in the body's hormones, including growth hormone, sex hormones, insulin, and thyroid. Since there are a number of medical issues in Prader-Willi syndrome that involve the hormone system, an endocrinologist who is familiar with PWS and who can work with the child or adult on all of these issues would be the best choice. Usually, a referral from the pediatrician or regular doctor usually is needed in order to see an endocrinologist.

How is the need for growth hormone evaluated?

The endocrinologist will likely review the medical history and growth of the child (often before age 2), ask about the child's diet, take information about other family members' heights and growth patterns, and examine the child. Endocrinologists take careful measurements of a child's height using a wall-mounted ruler for older children or will use a special measuring board to measure length for children under 2- to 3-years-old. Typically, individuals are measured several times at the same visit to ensure accuracy. Results are recorded both on standard growth charts and on PWS specific growth charts to determine how the child's height compares with others of the same age and with expected height velocity based upon the heights of their parents. Many children with PWS start out growing along the normal curve but then, at around age 2, begin growing more slowly and drop lower and lower on the standard growth charts. Children with growth failure associated with PWS usually are significantly shorter than their peers or are shorter than would be expected for their family.

Other tests that might be done as part of a pre-GH treatment evaluation include blood tests to check the level of thyroid hormones (low thyroid levels can affect growth and GH treatment), a hand x-ray to determine bone age, a physical exam for scoliosis (curvature of the spine), and a sleep study to check for obstructive sleep apnea, central sleep apnea, shallow breathing (hypoventilation) and carbon dioxide and/or oxygen levels. While the first line of treatment for obstructive sleep apnea in children is frequently the removal of their large tonsils and adenoids (adenotonsillectomy), individuals with PWS are at increased risk for residual apnea postoperatively and therefore should have a repeat sleep study. The hand x-ray for bone age is compared with a set of standard x-rays for different ages and can tell the doctor how much longer the child has left to grow. Children with growth hormone deficiency typically have a bone age that is younger than their actual age. If scoliosis is suspected, a back x-ray should be taken and examined by an orthopedic specialist to determine the exact degree of curve and the need for monitoring or treatment.

If a child with PWS is found to have growth failure, and there are no conditions that would create serious risks (such as cancer), he or she would be eligible for treatment with growth hormone without further testing. Children with Prader-Willi syndrome no longer need blood tests to prove they have

growth hormone deficiency before they can be treated with GH.

In 1996, the FDA approved the use of GH replacement therapy in adults, but unlike the 2000 FDA authorization for children with PWS, adults with PWS are required to document GH deficiency (GHD) by GH stimulation testing before considering treatment.

At what age are children assessed for GH treatment?

A child with PWS can be assessed for GH treatment at any age. Clinical experience suggests that GH treatment can be beneficial for an individual with PWS as early as 2 to 3 months of age.

Treatment intended to increase height needs to begin before the normal age of puberty, and earlier treatment (often prior to age 2) seems to offer the best opportunity for improvements in body composition and acquisition of motor milestones.

Short stature may not be apparent in the earliest years of life because infants with PWS often are born with normal length. However, there may be other signs of growth failure or GH deficiency that call for very early treatment such as a slowing of the rate of growth.

Are there any children who should not be treated with GH for medical reasons?

Because GH treatment stimulates growth throughout the body, children with diagnosed active cancer or tumors that could worsen are not good candidates for GH therapy.

Children with diabetes or glucose intolerance need to be closely monitored if they are treated with GH, since GH therapy is known to increase insulin resistance.

GH replacement therapy is not a substitute for the required dietary and weight management needs of affected individuals. Thus, for many children starting GH therapy as toddlers or young children, obesity may need to be addressed before GH treatment can be instituted.

Since children with PWS have “an increased prevalence of respiratory dysfunction,” a sleep study may be recommended before starting GH treatment with a follow-up sleep study six to eight weeks later. If sleep apnea is present and worsens after starting GH treatment, it should be managed appropriately and quickly, including seeing an ear/nose/throat doctor (otolaryngologist) to evaluate the airway and making efforts to lose weight if the child is obese. It is up to the discretion of the treating endocrinologist to determine if GH treatment should be temporarily discontinued until the sleep apnea is adequately treated.

How is GH administered?

Currently, growth hormone treatment must be administered by an injection similar to insulin injections for diabetes. GH injections are given just under the skin (subcutaneously rather than in the muscle). The shots are given with a very fine needle and typically are not painful. They can be given in a number of different areas of the body — the abdomen, the top and sides of the thigh, the buttocks, and in larger children the back of the upper arm. The injection should be given in a different spot each night to prevent skin problems.

The reason for rotating injection sites is that repeated injections at the same site may cause atrophy (loss of fat/muscle). Atrophy can lead to skin depressions (a cosmetic issue) and scarring, which can inhibit the absorption of medication and a diminished therapeutic response. It is adequate to rotate back and forth between two sites, such as the thighs, buttocks, and right and left abdomen. Even within a 2-inch by 2-inch single site, one can make an imaginary grid of quarter-inch squares to move across.

Growth hormone shots usually are given daily by parents, caregivers, or the individual him or herself. Nighttime is recommended because the largest natural spurt of growth hormone release occurs in the first few hours of sleep, so it is closest to the body's natural cycle. Families generally find it easy to make the injection part of the regular bedtime routine. A long-acting GH, once a week has been recently FDA approved but clinical trials will be needed before using it in PWS.

How do families learn to give the injections?

Family members and caregivers who will be giving the GH injections must be trained in how to mix the medication (if necessary), how to prepare and give the injection, and how to properly handle and store the GH product and injection equipment. A number of different pen-type syringes are available that make injections simpler for the parent or caregiver and less worrisome for the child who dislikes needles.

When families start their children on growth hormone treatment, they are normally provided with personal training, printed information, and telephone numbers to call in case they have questions or need help. They usually have an opportunity to practice using the syringe or injection pen and to give their child the first GH injections under the supervision of a nurse. The growth hormone supplier also might provide an instructional video to review at home. It is important to follow the manufacturer's directions since each type of injection method requires somewhat different procedures.

Although the thought of giving a child an injection may sound frightening, children and their parents usually learn and adjust to the routine quickly. Getting through the first injection at home is often the hardest part. It helps to remember that most GH shots are virtually painless. Also, since many children with PWS have a high pain tolerance, they are less likely than others to feel the injection. Information from the Human Growth Foundation and the MAGIC Foundation can help families understand GH treatment better and prepare themselves and their child to get started on a positive note. Both of these organizations have e-mail discussion lists for parents who want to ask questions or share information and support concerning GH treatment.

Are there different kinds of GH?

Although growth hormone medication is sold by a number of companies in the United States under different product names, the basic protein ingredient is the same in nearly all GH products for injection. Because it is based on the human gene for growth hormone, manufactured GH is identical in structure and chemistry to the growth hormone produced in the body. The generic name for the major synthetic GH product now in use is somatropin, which is not to be confused with the medical name for naturally occurring GH somatotropin. Somatropin is an "rDNA" (recombinant DNA), meaning that it is produced by combining DNA material from different sources through genetic engineering.

While the GH protein molecule itself is the same from product to product, there is an increasing variety of medication forms and injection devices available. In its basic, manufactured form, GH is a freeze-dried white powder that must be mixed with liquid, called a diluent. Some manufacturers now have pre-mixed forms of GH and/or pens that simplify the mixing process. As with other types of medicines, GH products may contain inactive ingredients such as preservatives. These additives vary among the different products, and some might cause minor reactions in some people. Most GH products require refrigeration before mixing and use, but a few can be left at room temperature until the powder is reconstituted (mixed with the diluent).

FDA approval of three GH products for Prader-Willi syndrome (Genotropin®, Omnitrope®, and Norditropin®) has opened the door for doctors to prescribe all three as equivalent products. Doctors might recommend a particular medication based on any of the following: the doctor's familiarity or experience with different GH products or delivery systems, requirements or preferences of the patient's insurance company or managed care organization, cost differences, ability of the family to learn and use a particular medication mixing and injection method, or the child's history or sensitivities. Families should discuss their concerns and needs with the doctor to ensure that the best treatment is chosen for their child's situation.

How is a child's dose of GH determined?

The standard recommended GH dose is from 0.18 to 0.24 mg/kg of ideal body weight divided 7 days a week. Infants should be started with the lowest GH dose, preferably during first 6 months of life.

The amount of IGF-1 detected in blood by commercial laboratories is the combination of free (up to 3%) and bound to IGFBP3. This is the blood test most used to monitor GH dosing.

At the present time, GH deficiency must be confirmed by GH stimulation testing in adults who require the GH mostly for anabolic effect. IGF-1 and less frequently bone mineral density (BMD) could help to monitor GH dosing.

What about follow-up after treatment begins?

Once growth hormone treatment has begun, regular follow-up exams must be scheduled to evaluate results, check for side effects, and adjust the child's dosage when needed.

Endocrinologists typically check patients a minimum of every four to six months when they are receiving GH treatment. At each checkup, the child will be carefully measured for growth and have a general physical exam. Periodically, the follow-up visits may also involve tests for:

- Thyroid hormone levels (blood test);
- insulin or glucose levels (blood test);

- IGF-1 and IGFBP-3 levels (blood test);
- bone age (x-ray);
- scoliosis (physical exam or x-ray);
- secondary sexual characteristics (physical exam), such as pubic hair; and
- sleep apnea (sleep study).

It is important for families to follow through with these scheduled follow-up visits and to contact the doctor between visits if there are any problems with the treatment. GH treatment and follow-up is a team effort, and the child's or adult's family is a key part of the team. It is the family that must carry out the day-to-day treatment and be alert for any changes in the child that may need medical attention.

In addition to the family and the endocrinologist, other professionals may need to be involved as the individual responds to GH treatment. Since calorie needs may change with increased growth or improved muscle mass, a consultation with a dietitian should be considered to ensure proper balanced nutrition including vitamin supplementation if indicated to promote growth. Any specialists normally seen on a regular basis (e.g., eye doctor, dentist, orthopedist, physical therapist, etc.) should be made aware that the individual is starting growth hormone treatment. Knowing that there will be a period of rapid growth may affect how often those professionals will need to monitor or treat the individual in their area of specialty.

When does GH treatment end?

When to stop GH treatment? GH treatment for linear growth should be discontinued when near adult height has been attained or complete skeletal maturation, usually around bone age of 14.5 years and 16.5 years in girls and boys respectively. Continuing GH treatment aimed at more growth in height after the bones have stopped growing can lead to overgrowth of some body parts, including the feet, hands, lower jaw, and eyebrow ridges, a condition called acromegaly. However, research has shown that growth hormone deficiency (GHD) can cause problems beyond the growing years — poor body composition, reduced energy and physical performance, osteoporosis (thinning bones), and disorders of sleep and mood.

As previously indicated, because the FDA approval for the use of GH in individuals with PWS is limited to “children”, adults with PWS may need to have documented growth hormone deficiency in order to be treated or continue treatment with growth hormone. Children who have been on growth hormone treatment through their final years of growth typically stop GH injections for a period of three to six months, then take a GH stimulation test to determine if they have growth hormone deficiency, as defined for adults. GH stimulation tests check the level of GH in the blood before and after the person is given a substance known to cause release of growth hormone (e.g., insulin, arginine, clonidine, or glucagon). This remains an area of controversy as most GH stimulation tests stimulate the pituitary gland to release GH instead of trying to stimulate the hypothalamus to release the GH releasing hormone. Since the hypothalamus is usually the part that is not properly working, this often gives a false positive picture of the GH production in affected individuals.

GH treatment in adults is provided at a much lower dosage level than in children. As with children, GH dosing for adults needs to be individualized, with close monitoring by specialists for unwanted side effects.

What are the cost and insurance issues?

Growth hormone is a very expensive medication, often costing \$50,000–\$60,000 a year at the highest dosage levels. Most families could not even consider GH treatment without excellent insurance coverage or other outside funding. If a family's insurance policy has an annual or a lifetime cap on benefits, the cost of one child's GH treatment over a long period of time could leave insufficient plan benefits for another family member who may need expensive care.

It is critical that families read carefully their insurance policies and any “riders” that amend the policies to determine what prescription drug benefits are provided, what is required for them to obtain GH treatment, and what limits have been set on either 1) prescription drug benefits or 2) total benefits payable. Because of rising prescription drug costs, insurance companies and managed care plans often try to limit their coverage in a number of ways. For example, a plan might specifically exclude or require special authorizations for expensive medications such as GH. Some provide coverage of “injectable” drugs under a different section of the plan that requires higher co-payment by the family. Others might set annual limits on how much they will pay for drugs, or they might require a higher co-payment from the family after a certain level is reached.

If a family's plan appears to cover GH treatment, but the initial insurance claim is rejected, an appeal can be filed for reconsideration of the claim. Every health plan has a process for submitting appeals and grievances, and each growth hormone company has a program to assist its patients with obtaining insurance coverage, if needed. *It is important to keep detailed notes of phone calls and copies of any documents related to an appeal or complaint.*

If the family's current plan does not provide adequate benefits to cover GH treatment, other insurance options may need to be explored. Finding an insurance policy that covers GH treatment can be difficult and may affect parents' employment options, since most insurance plans are provided through employers. (Information on Medicaid and State Children's Health Insurance Programs, which provide health insurance for families with lower incomes, is available on the Centers for Medicare and Medicaid Services of the U.S. Department of Health and Human Services Web site: www.cms.gov.)

Realizing that health insurance coverage is a major issue that may prevent a child from getting needed treatment, growth hormone manufacturers often supply the medication at no cost or at reduced cost for a limited period of time to eligible patients who are working to obtain insurance coverage or other funding.

Can an insurance company require that my child be tested for growth hormone deficiency (GHD) before they will cover GH treatment?

Health insurance plans are allowed to set their own requirements for coverage, but usually they will follow the U.S. Food and Drug Administration's (FDA) approvals. It should not be necessary for

a child with PWS to be tested for growth hormone deficiency since the FDA's decision regarding Prader-Willi syndrome, effective June 20, 2000. In creating these specific "indications" for children with PWS, the FDA recognized that GHD testing is not a reliable determinant of whether a child with PWS needs GH treatment. Those with PWS only need to show signs of growth failure and have a genetic diagnosis of PWS to qualify for GH treatment under these special Orphan Drug Act approvals. A letter from your doctor to the insurance company might help. For more information, see PWSA's announcement of the FDA ruling, reprinted in Appendix D.

5. QUESTIONS, WISDOM, AND SURVEY DATA FROM OUR FAMILIES

How can I find an endocrinologist to assess my child?

Ask your individual's primary care provider for suggestions. If you have a chapter of the Prader-Willi Syndrome Association in your state or region, ask members of that group for suggestions. Call several doctors and ask about having your child with PWS assessed for GH treatment. Also, ask how much experience they've had working with children with PWS. If you are unable to find a doctor with lots of experience in PWS, call PWSA | USA at (941) 312-0400 for information to share with your endocrinologist.

My child says the GH shots hurt. What can I do?

Although most children become accustomed to the injections, some children are more sensitive or find that certain injections hurt. Work with your endocrinologist's office to analyze what is causing the problem. There are many things that could cause discomfort, including the size of the needle, the type of injection device being used, the preservative in the medication, the temperature of the medication, the area of the body used for the shot, and the procedure used in giving the shot and removing the needle. If you cannot find a way to reduce the discomfort by changing one or more of these things, you can try rubbing a frozen spoon on the injection site prior to giving the dose. This will provide a quick numbing effect. You can also talk to your doctor about trying a cream to numb the skin prior to giving the shot.

Many children interpret fear as pain. A very small reward given after each shot, such as a sticker, can help to make the routine more positive. Too much anticipation, or randomness in a routine, can build up worry about an injection. Resisting, crying, or stalling are all normal coping behaviors and can even become part of the "routine" for some children. Some families find that giving the injection after the child is asleep decreases stress for everyone. This is a difficult choice to make, and you may want to talk with your health care provider if this seems like your best option. Finally, if the time after the injection seems to be normal, do not worry too much if the child does not like receiving shots. This may be nothing more than normal child behavior.

Are there natural GH supplements that my child could take instead of getting shots?

There are no oral forms of growth hormone and, although many nonprescription supplements and pills are being promoted today as growth enhancers or GH releasers, most have not been tested for effectiveness in individuals with PWS. Further, since these supplements are not regulated by the Food and Drug Administration, there is no way of knowing their actual content, effects, or safety.

Some GH manufacturers are trying to develop alternative ways to deliver GH to the body, and we may eventually see forms of synthetic growth hormone that can be taken orally or through the nostrils. If these products do come to market, they will be prescription drugs regulated by the FDA.

Parents Wisdom

Getting Started

Parents often are the best sources of solutions and answers to the little questions that arise when starting GH treatment. For example, parents from several e-mail discussion lists offered the following bits of wisdom:

- “At first, my wife and I did the shots together. This way we made sure we were doing everything correctly. The first few times you have to read and re-read the instructions to make sure you do everything correctly. Expect to be nervous the first few times. I promise you, it gets easier.”
- “Put the baby on the floor, not the bed. The bed is too soft and it’s too easy for him to move around. Have one parent hold his arms and legs to keep him from moving. The shot doesn’t seem to bother him, but kids are active!”
- “Mikey was only 21 months old when he started on GH. We just told him he was going to get a shot every night. My hubby holds Mikey down while I give the shot. We have the injector pen with the needle cover, so I never actually see the needle go in. That helps me a lot! Mikey is very used to the shot now. After we finish the counting and we pull the needle out, he says, ‘All done!’”

Travel Tips

Since most GH products must be refrigerated, traveling with a child on GH treatment can pose some interesting problems. A travel bag usually comes with the first GH prescription from the supplier. It can hold a small ice pack, the GH medication, and some injection supplies. After a certain amount of time, however, the medication needs refrigeration or a fresh ice pack, so planning ahead is critical. Ask the GH supplier about specific temperature requirements for your product. Following are some parent tips for traveling with supplies of GH:

- “Most hotels can get you a refrigerator for your room. This is especially helpful for longer hotel stays. Otherwise use four zip-lock bags, and put the pen in an ice chest or the ice bucket. Don’t count on one zip-lock bag keeping the pen dry in an ice chest. They leak.”
- “Most places will have a refrigerator somewhere. Carry some extra reusable ice packs and ask the hotel desk or restaurant to freeze them for you. Put them in a labeled bag. When your GH travel bag needs a fresh ice pack, stop at the desk or restaurant, and ask them to switch packs for you. When they know it’s for a child’s medication they’re usually accommodating.”
- “Keep an empty water or soda bottle with a screw cap to store the used needles or syringes until you can dispose of them safely.”
- “Don’t ever use baggage check for medicines when traveling by plane!”

APPENDIX

- A. Overview of Prader-Willi Syndrome
- B. Information Resources on Prader-Willi Syndrome
- C. Glossary of Terms
- D. Historic June 2000 Announcement from PWSA | USA of FDA Genotropin® Approval
- E. Growth Hormone Treatment and Prader-Willi Syndrome:
PWSA | USA Clinical Advisory Board Consensus Statement, June 2009
- F. References
- G. Recommendations for Evaluation of Breathing Abnormalities Associated
with Sleep in Prader-Willi Syndrome, December 2003
- H. Milestone
- I. Charts

APPENDIX A.

OVERVIEW OF PRADER-WILLI SYNDROME

Prader-Willi syndrome (PWS) is a complex and uncommon genetic disorder that affects about one in every 12,000 to 15,000 people. It is a lifelong condition that can be life-threatening.

Genetics

PWS is caused by several different genetic errors on chromosome 15, all of which result in the loss of certain genes normally expressed only from the chromosome 15 received from the father. The most common forms are:

- Deletion — some genes are missing from the chromosome 15 inherited from the father (about 70 percent of cases)
- Maternal uniparental disomy (UPD) — the child received two chromosome 15s from the mother and lost the one from the father (about 25 percent of cases)

The remaining 3 to 5 percent involve rare errors that can be inherited and are the cause for the extremely rare cases of more than one child in a family having PWS. PWS usually is not passed down from parent to child, and there is no known way to prevent it. Genetic testing, including prenatal testing, is now available to confirm all cases of PWS and to identify the specific genetic cause and the risk of having another affected child.

Physical Characteristics

Although not present in every person with the syndrome, the following are common:

- short stature
- small hands and feet
- hypotonia (low muscle tone in resting muscles) and poor muscle development
- excess fat, especially in the central portion of the body
- narrow forehead, almond-shaped eyes, and thin, down-turned lips
- light skin and hair, compared with other family members (especially in those with the chromosome 15 deletion)
- lack of complete sexual development in adolescence (e.g., small genitals, delayed menses)

Major Challenges of PWS

Although children and adults with PWS have many wonderful qualities, they and their families face significant challenges throughout life:

- **Early growth and development** — Infants often require assisted feeding efforts, including tube-feeding, to avoid failure to thrive. Major motor milestones (sitting up, walking, forming sentences, etc.) usually are delayed, and early intervention therapies often are needed to help develop motor, speech and learning skills.
- **Learning** — The child with PWS usually has some degree of learning and attention difficulties, requiring special education support throughout the school years.

- **Physical ability** — Weaknesses in muscle tone, strength, and motor planning skills make it difficult to gain coordination and speed for normal childhood activities and competitive sports. Since regular exercise is essential for weight control, sports modifications and alternate activities must be found and encouraged.
- **Weight control** — From early childhood, people with PWS require fewer calories than average to maintain reasonable weight, but they usually develop a greater-than-average appetite. Scientists suspect that PWS affects the brain's appetite control center, preventing the person with PWS from feeling full after eating. Until there are more effective medications to reduce appetite, those with the syndrome need other people to restrict their access to food so that they won't overeat. This requires careful meal planning and vigilance at home, day care, school, work, recreation and all other daily environments.
- **Behavior** — There are common behavior difficulties in people with PWS besides the urge to overeat. These may include obsessive-compulsive actions, changeable moods, sleepiness and under-activity, resistance to change, temper outbursts and skin-picking. Dealing with these behaviors requires consistent strategies and supports and sometimes medication. In spite of these potential problems, children and adults who have Prader-Willi syndrome are sweet and loving most of the time.

Major Medical Concerns

Conditions that are common in PWS and might require medical treatment include:

- obesity and its resulting problems, including Type 2 diabetes;
- respiratory weakness, of particular concern in infants and those with obesity;
- sleep apnea (periods of not breathing during sleep);
- osteoporosis (thinning of bones) in children and adults, leading to fractures;
- scoliosis and kyphosis (abnormal curves of the spine); and
- strabismus (crossed eye).

Growth hormone therapy offers a number of health benefits for individuals with PWS, including improvements in height, body composition, respiration, physical activity level and bone density.

Additional Cautions

In monitoring health, families and care providers should be aware of these common characteristics in people with PWS:

- reduced sensitivity to pain;
- temperature instability;
- possible bone fragility and decreased pain sensitivity, leading to undiagnosed fractures;
- absence of normal vomiting reflex; and
- sensitivity to normal doses of some medications.

For more information on Prader-Willi syndrome, see information resources in Appendix B.

APPENDIX B.

INFORMATION RESOURCES ON PRADER-WILLI SYNDROME

Prader-Willi Syndrome Association | USA

Formed in 1975, Prader-Willi Syndrome Association | USA (PWSA | USA) unites individuals, parents, professionals, and others to enhance the quality of life of those affected by Prader-Willi syndrome. PWSA | USA empowers the PWS community through shared experiences, research, education, advocacy, and support. Our purpose is to assist individuals living with PWS and their families every step of their journey.

Contact PWSA | USA

1032 E Brandon Blvd #4744,
Brandon, FL, 33511
Phone: (941) 312-0400
Email: info@pwsausa.org
Website: www.pwsausa.org

PWSA | USA's website contains an extensive amount of information on issues such as medical, genetics, school support, research, crisis support and general health care guidelines for individuals with PWS, as well as links to other sources of information and support.

APPENDIX C.

GLOSSARY OF TERMS

Following are definitions of some of the terms used in this publication and in the clinical research summaries.

BIA

Bioelectrical impedance analysis; use of an electrical charge to measure fat in the body (fat tissue resists electricity); considered to be less accurate than DEXA scan

body composition

Proportions of body weight made up of fat, muscle, bone, etc.

bone age

Stage of development of the bones, evaluated by comparing a hand x-ray to a series of reference x-rays for specific chronological ages; used to determine skeletal growth potential

bone mineral density (BMD)

Thickness, strength of internal bone structure

BMI

Body mass index, a formula used to determine obesity; calculated by dividing a person's weight (in kilograms) by the square of their height (in meters)

CAT scan

Computerized axial tomography, now known as computed tomography or CT scan; a type of x-ray that films cross sections of the body to measure masses and body composition

Centimeter (cm)

A metric unit of linear measurement equal to 0.39 inches (1 inch = 2.54 cm)

Control group

Participants in a study who receive no treatment; used to compare results with the treated group

CT scan

Computed tomography, a type of x-ray that films cross sections of the body to measure masses and body composition; also referred to as CAT scan

DEXA scan

Dual-energy x-ray absorptiometry, a low-level x-ray used to measure body composition and bone density

Endocrine

Referring to the body's system of hormones and the glands that produce and release them into the bloodstream

Endocrinologist

A medical doctor who specializes in disorders of the endocrine system

Fat-free mass

The portion of body that is not fat, including muscle, bone and water

GH

Growth hormone, a protein hormone made and stored in the pituitary gland and released into the bloodstream in response to GHRH; also called somatotropin

GHD

Growth hormone deficiency, a lack of sufficient growth hormone in the body

GHRH

Growth hormone releasing hormone, the messenger hormone sent by the hypothalamus to the pituitary gland, prompting it to release growth hormone

GH stimulation test

Measurement of GH in the bloodstream following administration of one or more substances known to stimulate growth hormone release; also called provocative GH testing

Height velocity

The rate of height growth, usually measured in centimeters per year

HGH

Human growth hormone produced in the pituitary gland, as distinguished from the synthetic form

Hypothalamus

The part of the brain that connects the nervous system and the endocrine system; the hypothalamus is connected to the pituitary gland and gives it the commands to make and release growth hormone

IGF-1

Insulin-like growth factor-1, a protein hormone produced by the liver in response to growth hormone; IGF-1 directly causes growth in skeletal and muscle cells; IGF-1 is also called somatomedin-C

IGFBP-3

IGF binding protein-3; the substance that carries IGF-1 throughout the body to promote growth

IU

(also written as MU) International unit; a weight measurement equal to 0.33 milligrams (1 mg = 3 IU)

Kilogram (kg)

A metric unit of weight measurement equal to 2.2 pounds (1 pound = 0.45 kg)

Linear growth

Growth in height

Liver

The major target organ for GH; in response to GH in the bloodstream, the liver produces IGF-I and releases it to promote growth in bones and muscles

Meter (m)

A metric unit of linear measurement equal to 39.37 inches or 100 centimeters

Meters Squared (M²)

Meters squared; a computation of body surface area

based on a person's weight and height; sometimes used to calculate GH dosage, especially when weight is high for the person's height

Physis

Also called the growth plate, is a layer of cartilage near the ends of bones where new cell growth occurs in children, causing the bone to grow in length. When the physis closes, all cartilage has hardened into bone and no further growth is possible.

Pituitary gland

The "master" endocrine gland that makes and releases growth hormone into the body as well as a number of different hormones that stimulate the other endocrine glands; the pituitary is connected to and controlled by the hypothalamus

Pulmonary function test

A non-invasive test that shows how well the lungs are functioning.

Recombinant Growth Hormone (RGH)

A biosynthetic hormone that is identical to human growth hormone, but it is synthesized in the lab

Resting energy expenditure (REE)

Metabolic rate (calorie usage) during rest to keep vital body functions going, such as breathing and keeping warm, also known as the Basal Metabolic Rate (BML).

SD

Standard deviation; a unit of measure to describe how much a given number is below (-) or above (+) the average for a certain group; 2 SD is the difference between the 50th and the 3rd percentile on a growth chart

Skinfold thickness

A physical measurement of body fat, using a tool called caliper to determine the thickness of flesh (skin) at specific areas of the body

Somatropin (rDNA origin)

The medical name for synthetic growth hormone products that are identical in molecular structure to human growth hormone

APPENDIX D.

HISTORIC JUNE 2000 ANNOUNCEMENT FROM PWSA | USA OF FDA GENOTROPIN® APPROVAL

June 2000

Dear PWSA | USA Member,

As we have all been aware, for years there has been no medication specifically approved for individuals with Prader-Willi syndrome (PWS). Now, finally, there is some good news. We are pleased to inform you that the U.S. Food & Drug Administration (FDA) has just determined that PWS is an “indication” (eligible condition) for treatment with Genotropin™ (somatropin rDNA for injection), which is a form of growth hormone manufactured by Pharmacia Corporation. Previously approved to treat “growth hormone deficiency” in children and adults, Genotropin is now the only treatment approved specifically for “growth failure in children with PWS.”

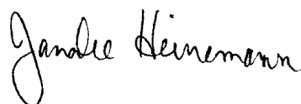
This does not mean that there is a problem if your child is on another brand of growth hormone. In general, growth hormone therapy has been approved for some time – but now, Genotropin specifically has been approved for treating PWS. Genotropin’s approval for PWS was issued by FDA under the Orphan Drug Act. (This designation is only given to treatments for which the potential patient population is under 200,000. Orphan Drug status entitles Pharmacia exclusivity in marketing the drug for this purpose for the next seven years.) FDA approval should make it easier for families to appeal to insurance companies for coverage and should help with Medicaid coverage. Also, under the FDA ruling, growth hormone deficiency testing will no longer be required for children with PWS and growth failure who are being considered for GH treatment.

Results from the studies submitted to the FDA reveal that growth hormone treatment improves growth and body composition in children with PWS, including stimulating skeletal growth, decreasing the amount of body fat and increasing lean body mass (muscle). Given the many issues faced by families affected by PWS, we believe the increased availability of growth hormone will be of benefit to many members of our community by helping to reduce some of the major medical problems often inherent in this syndrome. Please note that you should consult with your physician as to whether growth hormone therapy is appropriate in your particular case, since it may not be beneficial for every child with PWS.

By the end of the year PWSA (USA) will publish a new booklet for parents and guardians, designed to help you make informed decisions about growth hormone treatment. When it is available, we will inform you through our newsletter, The Gathered View. Meanwhile, you can refer to the enclosed consensus statement and log on to our website at www.pwsausa.org. If you would like more information specifically about Genotropin or its use in PWS, please feel free to visit the Genotropin website (www.genotropin.com) or call 1-800-645-1280.

It is a new era for Prader-Willi syndrome with many encouraging things on the horizon! We are enclosing further “cutting edge” information on growth hormone therapy and will do all we can to keep you informed of all new treatment options.

Sincerely,



Janalee Heinemann, MSW
Former Executive Director, PWSA | USA

Editor's Note: in April 2010 the FDA approved a second growth hormone treatment specifically for children with growth failure due to Prader-Willi syndrome. This latest product approval involves omnitrope®, manufactured by Sandoz, inc. See Appendix C for additional product information.

APPENDIX E.

GROWTH HORMONE TREATMENT AND PRADER-WILLI SYNDROME: PWSA | USA CLINICAL ADVISORY BOARD CONSENSUS STATEMENT, JUNE 2009

Since the commercial release of recombinant human growth hormone (GH) in 1985, therapeutic use of this medication has been studied in a variety of medical conditions and genetic syndromes. Based on current medical knowledge, the Clinical Advisory Board of the Prader-Willi Syndrome Association | USA has drafted and approved this policy statement to guide health care providers in the use of GH treatment in individuals with Prader-Willi syndrome (PWS). Currently, 60 percent of the individuals in the PWSA | USA database are receiving GH therapy.

Current considerations regarding the use of GH treatment in PWS can be divided into the following categories:

1. GH treatment of infants/children with PWS to improve body composition abnormalities and improve linear growth
2. GH treatment of adults with PWS to improve body composition abnormalities and improve bone mineral density

Numerous studies indicate that GH deficiency occurs frequently in children with PWS and that treatment with GH is efficacious in improving the growth and body composition of these children. GH should not be a substitute for appropriate nutritional intake and physical activity.

GH treatment is FDA-approved for individuals with PWS. It is well-recognized that GH deficiency is a part of PWS and that provocative testing for GH deficiency is not indicated for children with PWS because: 1) the results can be influenced by obesity; 2) different testing protocols give widely discrepant results; 3) the diagnostic boundary for normal/abnormal GH result in response to testing is still debated; and 4) there is no ideal testing protocol.

GH Treatment of Infants and Children with PWS

Multiple studies have documented the benefits of GH therapy in individuals with PWS, including, but not limited to, improvements in lean body mass, decreased body fat, increased bone mineral density, and normalization of adult height. Further, GH treatment in infants and children with PWS has been shown to improve strength, agility, and motor development. Treatment with GH has also been shown to positively affect nitrogen balance and increase energy expenditure in individuals with PWS. Moreover, GH treatment may help preserve lean body mass during caloric restriction. There is evidence that beginning GH therapy prior to 2 years of age is beneficial because of the positive effects of this treatment on mental and motor development.

The risks and benefits of GH treatment should be thoroughly discussed with the child's parents or guardians before making a decision to treat. At the same time, it should be stressed that GH therapy is only one treatment tool for their child and should be used in conjunction with appropriate nutritional intake and physical activity. GH treatment should not be viewed as a substitute for diet and exercise. Treatment should commence using standard dose guidelines (0.18 – 0.3 mg/kg/week) given as a daily subcutaneous injection with careful monitoring of clinical status at regular intervals. Standard GH treatment includes dose initiation and adjustment based on weight. However, there is some evidence that lean mass is a better indicator of GH requirements and, therefore, monitoring clinical growth and IGF-1 levels is helpful in determining dose adjustments. The Clinical Advisory Board recommends that the GH dose in children with PWS be adjusted on an individual basis rather than by specific criteria. Clinical monitoring should include nutritional status, height, weight and head circumference measurements; calculation of growth velocity; bone age; physical examination; and measurement of IGF-1, glucose, insulin and thyroid hormone levels, as well as ensuring adequate nutrition for growth and brain development. If feasible, assessment of body composition is also helpful.

Children with PWS have an increased risk for spinal curvature abnormalities, including scoliosis and kyphosis. In general, these findings may first become apparent or more rapidly progress during periods of rapid growth. There is no evidence that GH itself causes these abnormalities. Children with PWS, whether or not they are treated with GH, should receive a careful back examination at least annually. The decision to initiate or continue GH treatment in a child with spinal curvature abnormalities should be made in consultation with an endocrinologist and an orthopedic surgeon experienced in PWS, and after full discussion with the child's parents or guardians.

Children with PWS are prone to developing obesity and its associated complications, including glucose intolerance and type 2 diabetes mellitus. GH may induce insulin insensitivity. Therefore, children with PWS and GH deficiency should be carefully monitored for signs and symptoms of glucose intolerance during GH treatment, particularly if they are massively obese (e.g., >200% of ideal body weight) or have a family history of diabetes mellitus. Routine biochemical screening tests may include fasting blood glucose, urine glucose dipstick or HbA1c. If diabetes mellitus occurs as a result of GH therapy, the GH treatment should be stopped. If treatment is restarted, the dose of GH should be substantially reduced. If glucose intolerance occurs with GH therapy it can typically be treated with an oral hypoglycemic agent, such as metformin.

Children with PWS have an increased prevalence of respiratory dysfunction, which may be related to obesity, hypotonia or central respiratory drive abnormalities. Careful history and assessment of respiratory abnormalities should be evaluated prior to and during GH therapy. Individuals with sleep apnea, either before or after beginning GH therapy, should be evaluated by a pulmonologist, otolaryngologist, and gastroenterologist to determine if:

1. The apnea is mild or central in origin (in which case GH is not contraindicated).
2. If the apnea is severe and obstructive in origin, this needs to be addressed before GH is initiated.
3. There are confounding pre-existing conditions, such as morbid obesity, upper respiratory tract infection, adenoid/tonsillar hypertrophy, or gastroesophageal reflux that may exacerbate sleep-disordered breathing. In addition, some groups recommend that individuals with PWS have overnight polysomnography (sleep study) before and ~ 6-12 weeks after beginning GH treatment and if there is any worsening of clinical symptoms while on GH therapy.

GH Treatment of Persons who have Achieved Final Height and Adults with PWS

Recent studies indicate that adults with PWS also benefit from GH replacement therapy, with improvements in body composition, bone mineral density, and exercise capacity. Treatment doses are typically started at 0.2 mg/day and increased by 0.2 mg increments as necessary to maintain IGF-1 levels within the normal range for age and sex. The prevalence of GH deficiency in adults with PWS is not well-documented, but the problems surrounding provocative testing for GH deficiency are the same as described above for children. However, at this time in the U.S. insurance companies still require documentation of GH deficiency by provocative testing in adults with PWS.

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APPENDIX G.

RECOMMENDATIONS FOR EVALUATION OF BREATHING ABNORMALITIES ASSOCIATED WITH SLEEP IN PRADER-WILLI SYNDROME

PWSA | USA Clinical Advisory Board Consensus Statement December 2003

Problems with sleep and sleep disordered breathing have been long known to affect individuals with Prader-Willi syndrome (PWS). The problems have been frequently diagnosed as sleep apnea (obstructive [OSA], central or mixed) or hypoventilation with hypoxia. Disturbances in sleep architecture (delayed sleep onset, frequent arousals and increased time of wakefulness after sleep onset) are also frequently common. Although prior studies have shown that many patients with PWS have relatively mild abnormalities in ventilation during sleep, it has been known for some time that certain individuals may experience severe obstructive events that may be unpredictable.

Factors that seem to increase the risk of sleep disordered breathing include young age, severe hypotonia, narrow airway, morbid obesity and prior respiratory problems requiring intervention such as respiratory failure, reactive airway disease and hypoventilation with hypoxia. Due to a few recent fatalities reported in individuals with PWS who were on growth hormone therapy (GH) some physicians have also added this as an additional risk factor.

One possibility (that is currently unproven) is that GH could increase the growth of lymphoid tissue in the airway, thus worsening already existing hypoventilation or OSA. Nonetheless, it must be emphasized that there are currently no definitive data demonstrating that GH causes or worsens sleep disordered breathing. However, to address this new concern, as well as the historically well documented increased risk of sleep-related breathing abnormalities in PWS, the Clinical Advisory Board of the PWSA | USA makes the following recommendations:

- 1. A sleep study or a polysomnogram** that includes measurement of oxygen saturation and carbon dioxide for evaluation of hypoventilation, upper airway obstruction, obstructive sleep apnea and central apnea should be contemplated for all individuals with Prader-Willi syndrome. These studies should include sleep staging and be evaluated by experts with sufficient expertise for the age of the patient being studied.
- 2. Risk factors that should be considered to expedite the scheduling of a sleep study should include:**
 - Severe obesity — weight over 200 percent of ideal body weight (IBW).
 - History of chronic respiratory infections or reactive airway disease (asthma).
 - History of snoring, sleep apnea or frequent awakenings from sleep.
 - History of excessive daytime sleepiness, especially if this is getting worse.
 - Before major surgery, including tonsillectomy and adenoidectomy.
 - Prior to sedation for procedures, imaging scans and dental work.

- Prior to starting growth hormone or if currently receiving growth hormone therapy.

Additional sleep studies should be considered if patients have the onset of one of these risk factors, especially a sudden increase in weight or change in exercise tolerance. **If a patient is being treated with growth hormone, it is not necessary to stop the growth hormone before obtaining a sleep study unless there has been a new onset of significant respiratory problems.**

Any abnormalities in sleep studies should be discussed with the ordering physician and a pulmonary specialist knowledgeable about treating sleep disturbances to ensure that a detailed plan for treatment and management is made. Referral to a pediatric or adult pulmonologist with experience in treating sleep apnea is strongly encouraged for management of the respiratory care.

In addition to a calorically restricted diet to ensure weight loss or maintenance of an appropriate weight, a management plan may include modalities such as:

- Supplemental oxygen
- Continuous positive airway pressure (CPAP) or BiPAP
- Oxygen should be used with care, as some individuals may have hypoxemia as their only ventilatory drive and oxygen therapy may actually worsen their breathing at night.
- Behavior training is sometimes needed to gain acceptance of CPAP or BiPAP.
- Medications to treat behavior may be required to ensure adherence to the treatment plan.
- An exercise plan.

If sleep studies are abnormal in the morbidly obese child or adult (IBW>200%) the primary problem of weight should be addressed with an intensive intervention — specifically, an increase in exercise and dietary restriction. Both are far preferable to surgical interventions of all kinds. Techniques for achieving this are available from clinics and centers that provide care for individuals with PWS and from the national parent support organization (PWSA | USA). Behavioral problems interfering with diet and exercise may need to be addressed simultaneously by persons experienced with PWS.

If airway-related surgery is considered, the treating surgeon and anesthesiologist should be knowledgeable about the unique pre- and postoperative problems found in individuals affected by Prader-Willi syndrome (for the most recent recommendations visit www.pwsausa.org). **Tracheostomy surgery and management presents unique problems for people with PWS and should be avoided in all but the most extreme cases.** Tracheostomy is typically not warranted in the compromised, morbidly obese individual because the fundamental defect is virtually always hypoventilation, not obstruction. Self-endangerment and injury to the site are common in individuals with PWS who have tracheostomies placed.

At this time there is no direct evidence of a causative link between growth hormone and the respiratory problems seen in PWS. Growth hormone has been shown to have many beneficial

effects in most individuals with PWS, including improvement in the respiratory system. Decisions in the management of abnormal sleep studies should include a risk/benefit ratio of growth hormone therapy. **It may be reassuring for the family and the treating physician to obtain a sleep study prior to the initiation of growth hormone therapy and after 6-8 weeks of therapy to assess the difference that growth hormone therapy may make.** A follow-up study after one year of treatment with growth hormone may also be indicated.

Prader Willi-Syndrome Association | USA
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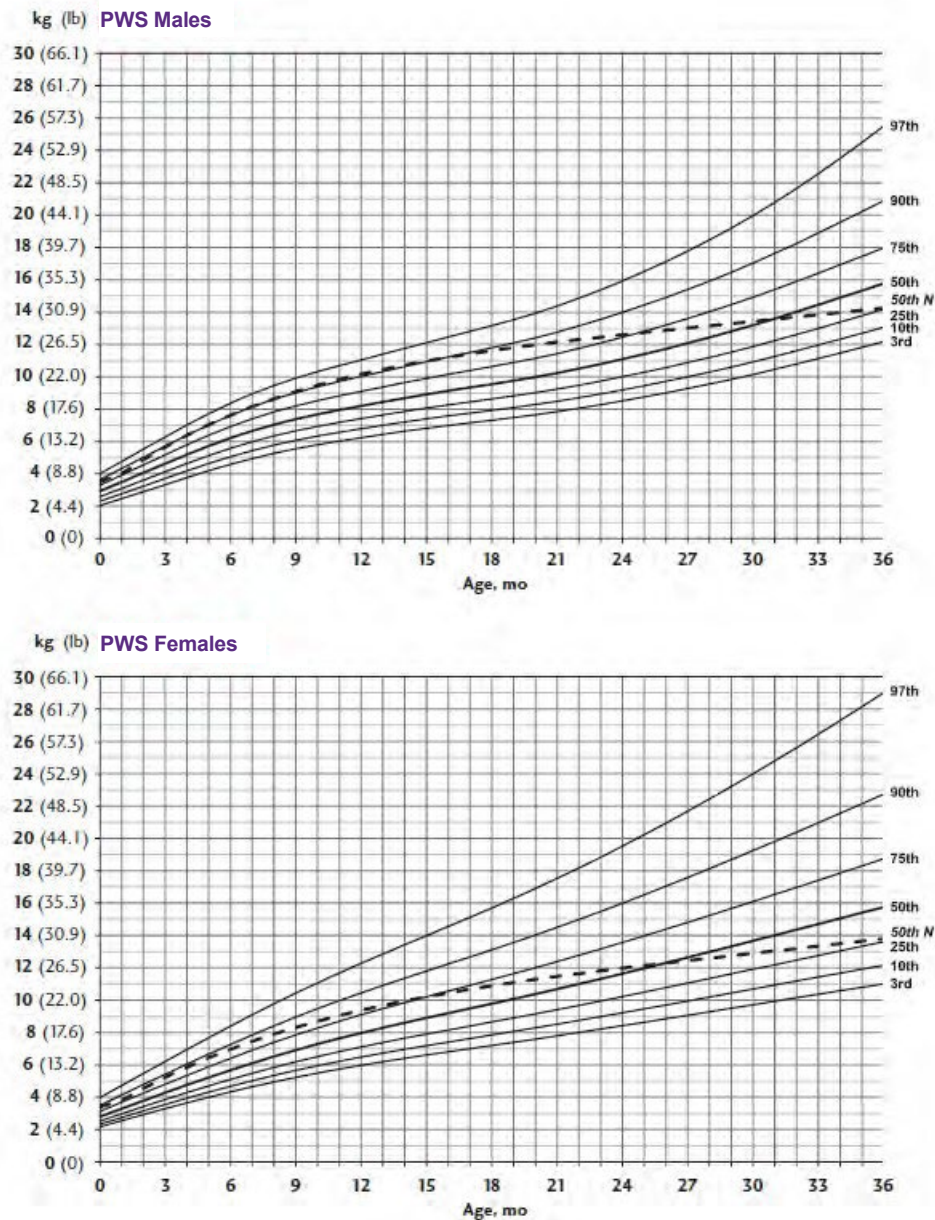
Telephone: (941) 312 0400
E-mail: info@pwsausa.org
Website: www.pwsausa.org

APPENDIX H. MILESTONES

- 1956** Prader-Willi syndrome (PWS) is first described in a published article by Swiss doctors Prader, Willi and Labhart
Human growth hormone is first isolated by scientists
- 1958** The first growth hormone injection is given to a human, using growth hormone extracted from the pituitary of a cadaver (deceased person)
- 1972** The chemical structure of human growth hormone is discovered
- 1985** Use of human growth hormone from cadavers is halted after several patients develop a deadly brain disease (Creutzfeldt-Jakob disease, or CJD) from contaminated extract
The first synthetic (manufactured) growth hormone is approved by the U.S. Food and Drug Administration (FDA) for treatment of children with growth hormone deficiency
- 1987** The first article on the effect of growth hormone treatment in PWS is published in a medical journal
- 1992** The first major presentation on growth hormone treatment in PWS is given at a PWSA | USA conference
- 1996** The FDA approves GH for treatment of adults with growth hormone deficiency
- 1997** Results of the first controlled scientific studies on GH treatment in PWS (in Europe) are published
- 1999** Results of the first U.S. controlled study of GH treatment in PWS are published
- 2000** The FDA approves the first GH treatment specifically for children with growth failure due to PWS (Genotropin®/Pfizer)
- 2010** The FDA approves a second GH treatment specifically for children with growth failure due to PWS (Omnitrope®/Sandoz)

APPENDIX I. CHARTS

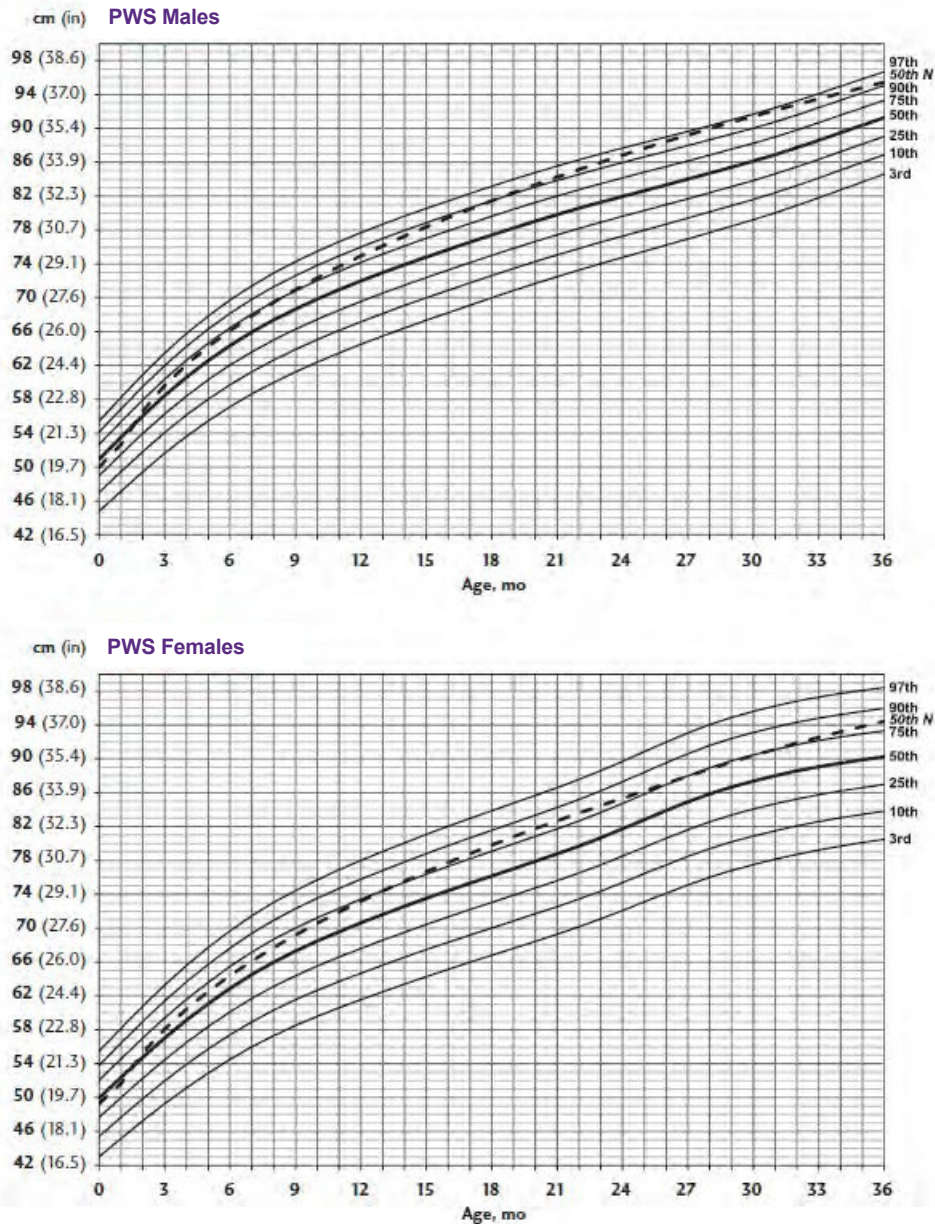
Weight of Infants with PWS Compared with Normal Weight for Age



Standardized curves for weight of male (upper) and female (lower) infants with PWS (solid lines) and normative 50th percentile (broken line).

“Growth Standards of Infants with Prader-Willi Syndrome,” by Merlin G. Butler, et al., are reproduced with permission from *Pediatrics* (the journal of the American Academy of Pediatrics), Vol. 127, May 2011, Pages 687-695, Copyright 2011 by the AAP.

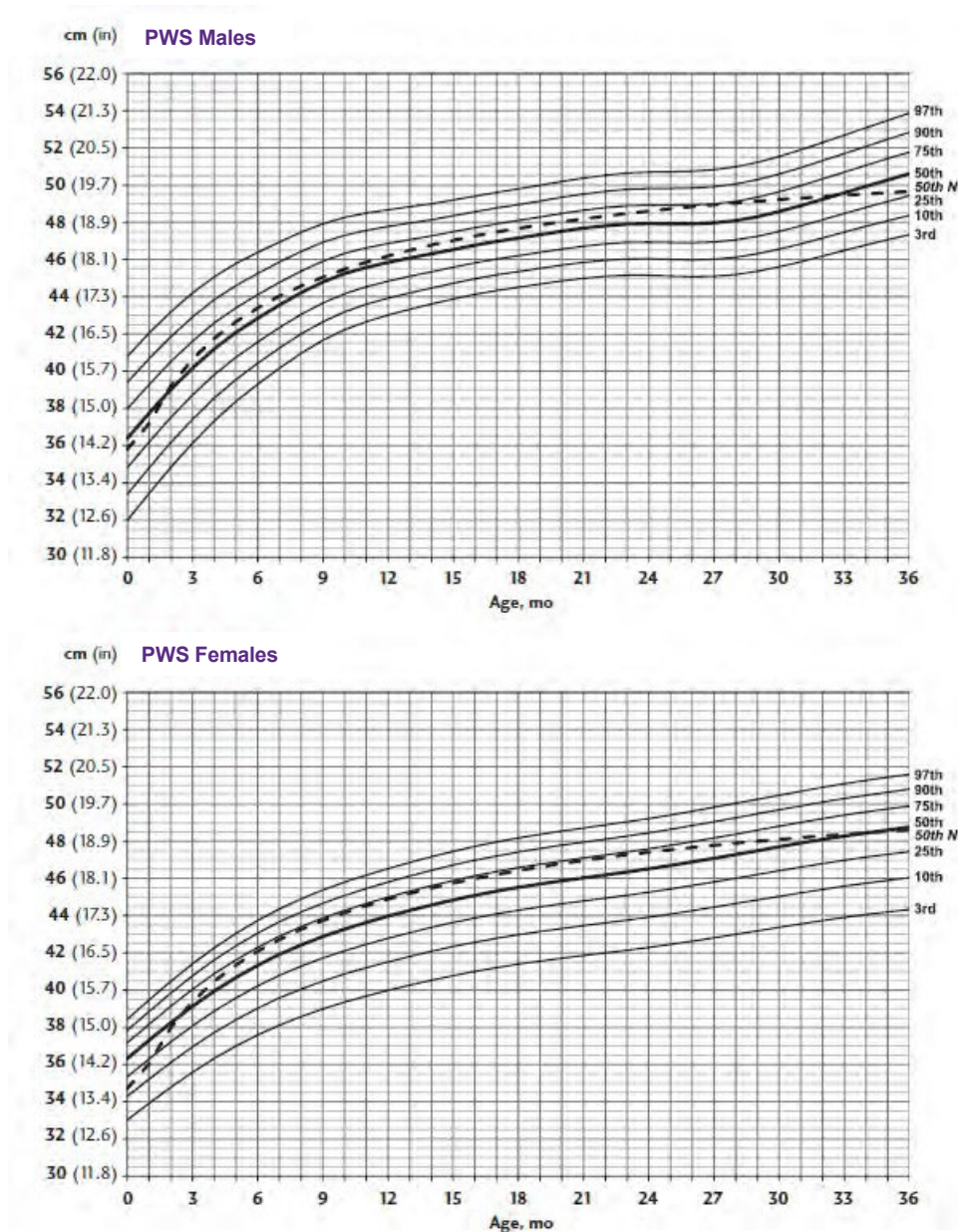
Length of Infants with PWS Compared with Normal Length for Age



Standardized curves for length of male (upper) and female (lower) infants with PWS (solid lines) and normative 50th percentile (broken line).

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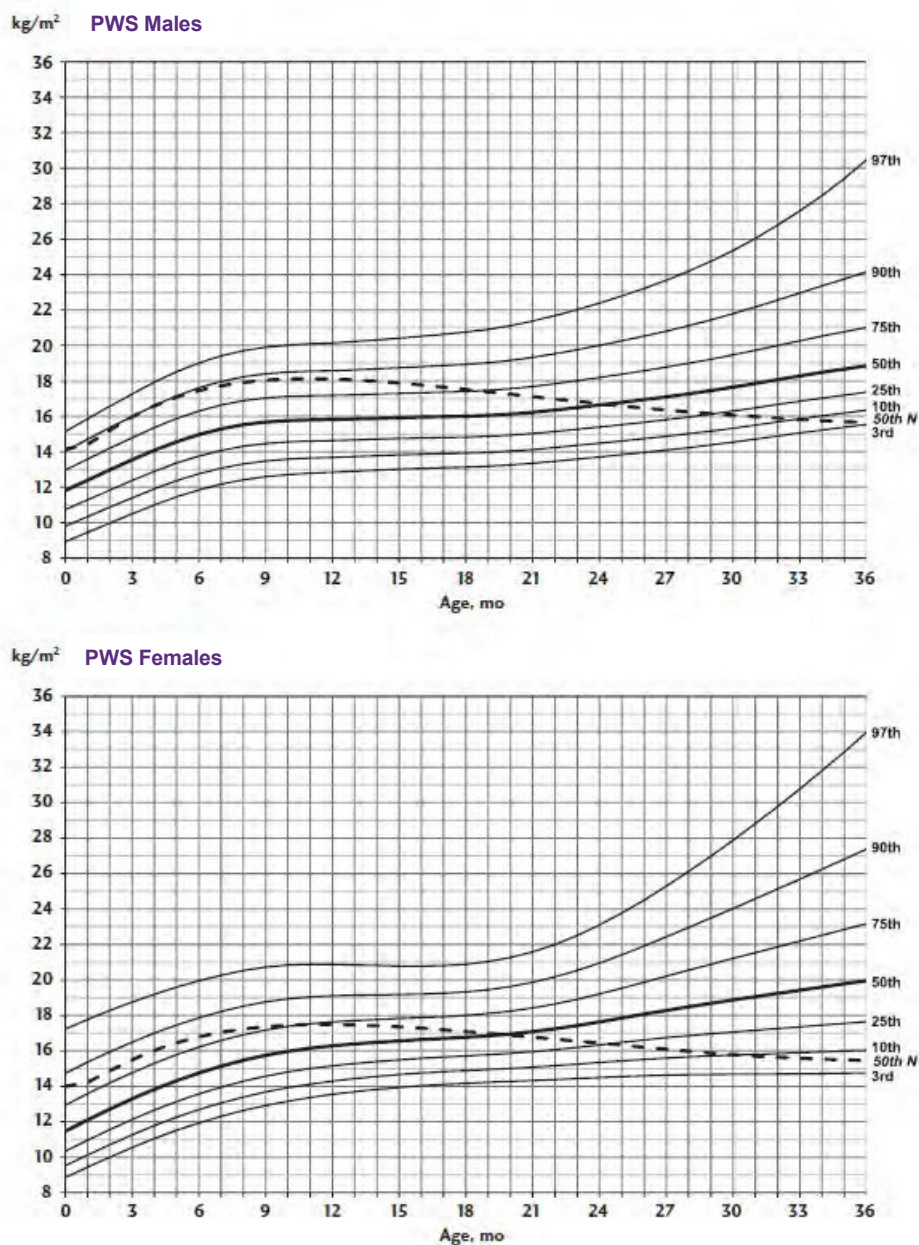
Head Circumference of Infants with PWS Compared with Normal Head Circumference for Age



Standardized curves for head circumference of male (upper) and female (lower) infants with PWS (solid lines) and normative 50th percentile (broken line).

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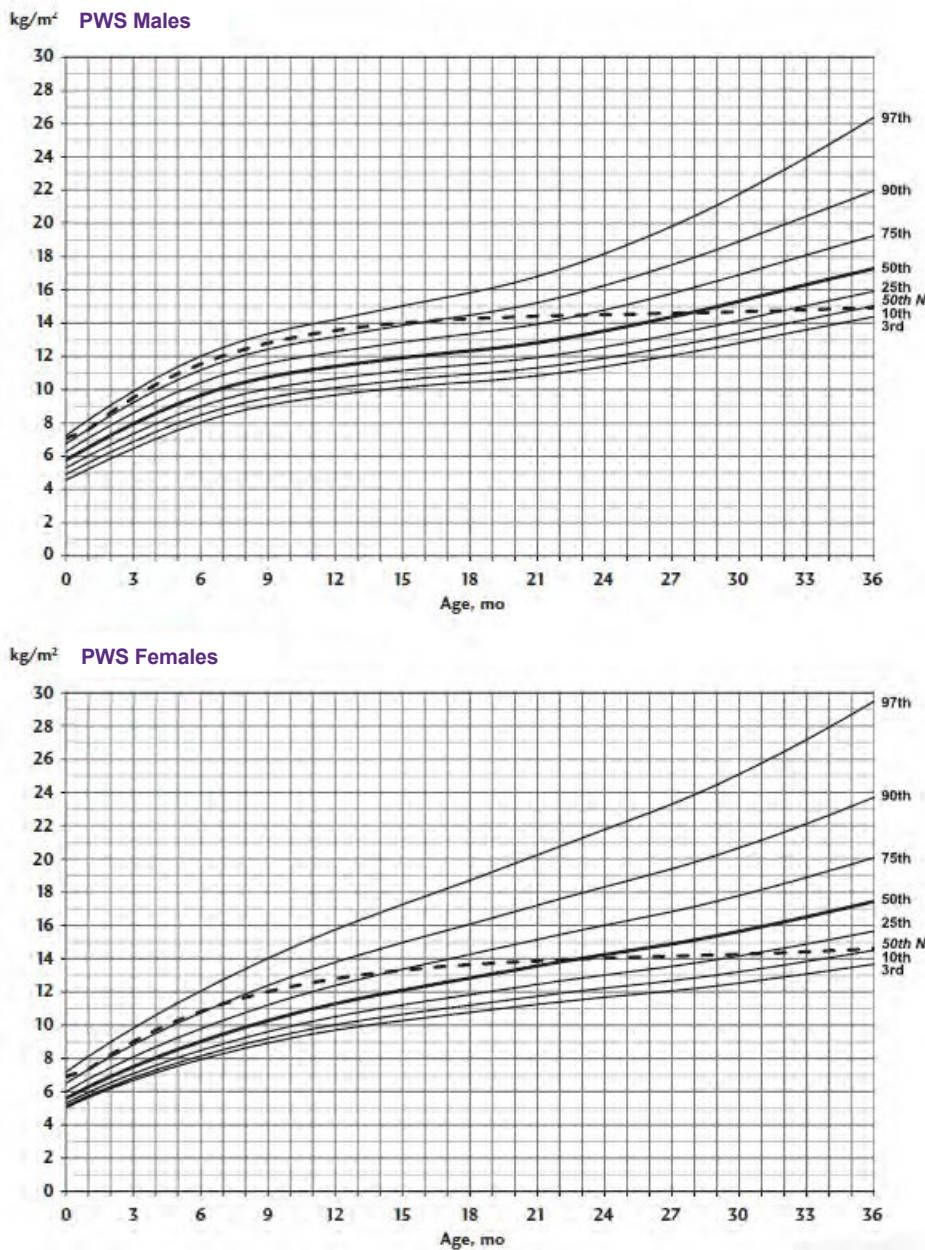
BMI of Infants with PWS Compared with Normal BMI for Age



Standardized curves for BMI of male (upper) and female (lower) infants with PWS (solid lines) and normative 50th percentile (broken line).

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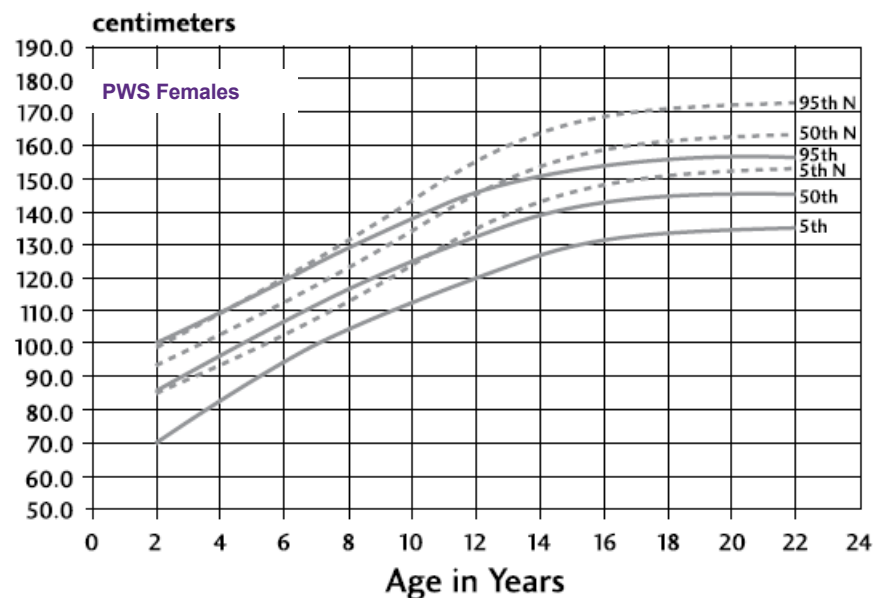
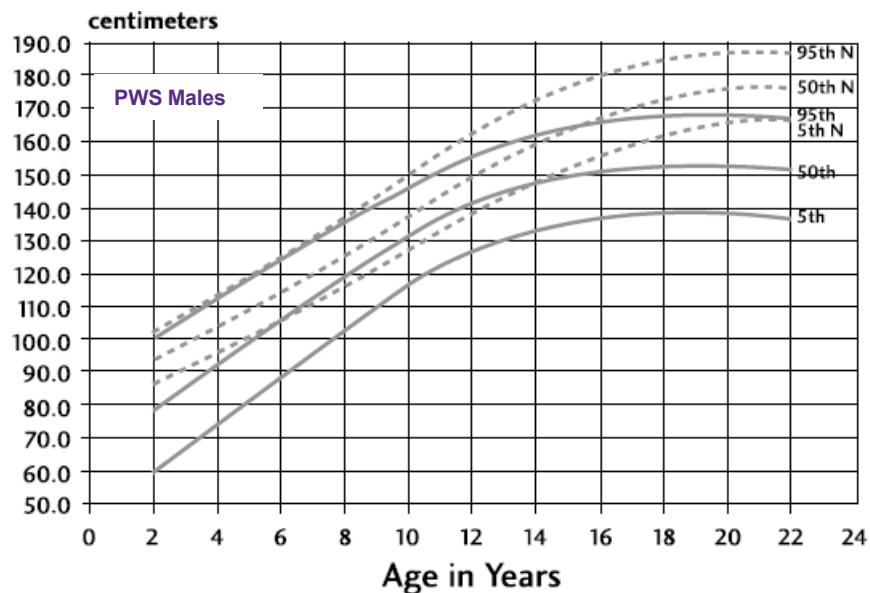
Weight/Length of Infants with PWS Compared with Normal Weight/Length for Age



Standardized curves for weight/length of male (upper) and female (lower) infants with PWS (solid line) and normative 50th percentile (broken line).

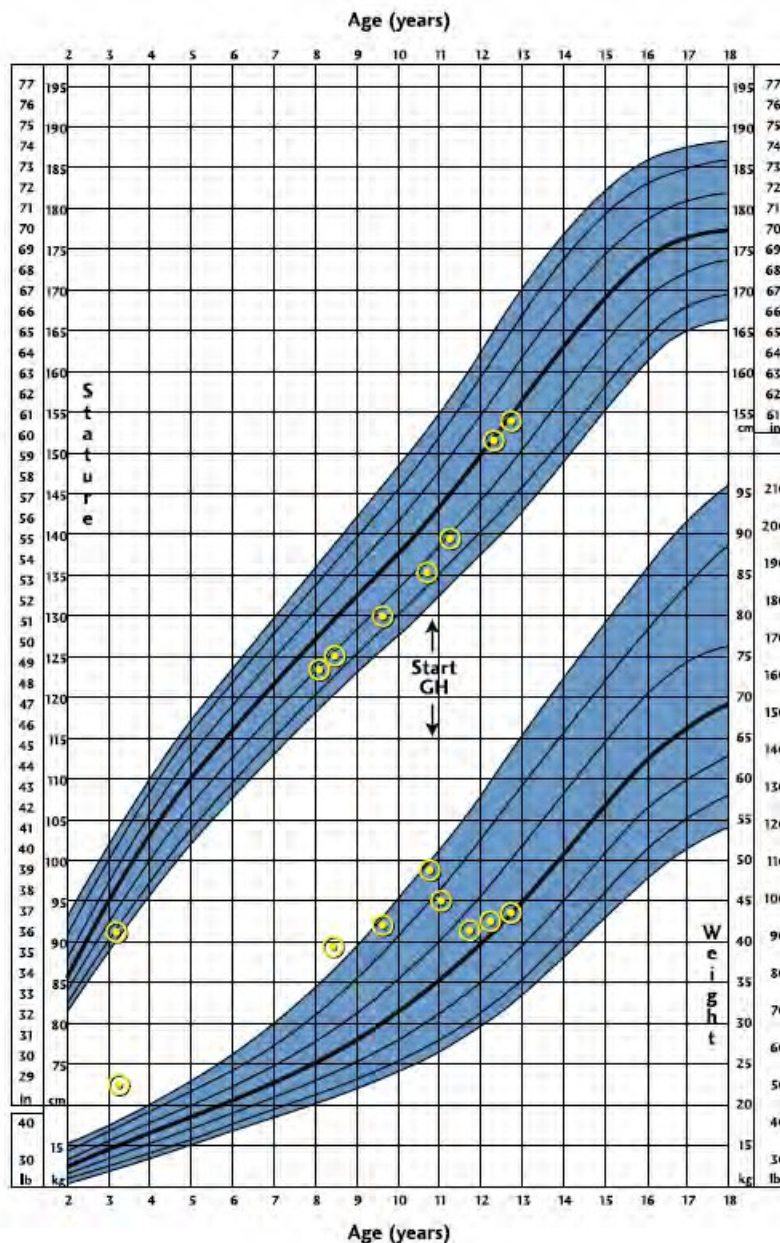
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Heights of Individuals with PWS Compared with Normal Heights for Age



Standardized curves for height of Prader-Willi syndrome (PWS) male and female patients (solid line) and typical individuals (broken line). (M.G. Butler and F.J. Meaney)
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Growth Chart of a Boy with PWS Who Began GH Treatment at Age 10



(Courtesy of Dr. Aaron Carrel, University of Wisconsin–Madison)

Note: Points show the height (stature) and weight of the boy at various ages, before and after starting growth hormone at 10 years of age. Shaded areas represent the ranges of height and weight for normal, healthy children. Lines on each growth curve represent the 5th, 10th, 25th, 50th (bold line), 75th, 90th and 95th percentiles.



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