

# GROWTH HORMONE AND PRADER-WILLI SYNDROME

S E C O N D   E D I T I O N



A REFERENCE FOR FAMILIES AND CARE PROVIDERS

Donald G. Goranson, Jr., Editor

USA  
PRADER-WILLI SYNDROME ASSOCIATION  
*Still hungry for a cure.*

USA  
**PRADER-WILLI SYNDROME ASSOCIATION**  
*— Still hungry for a cure. —*

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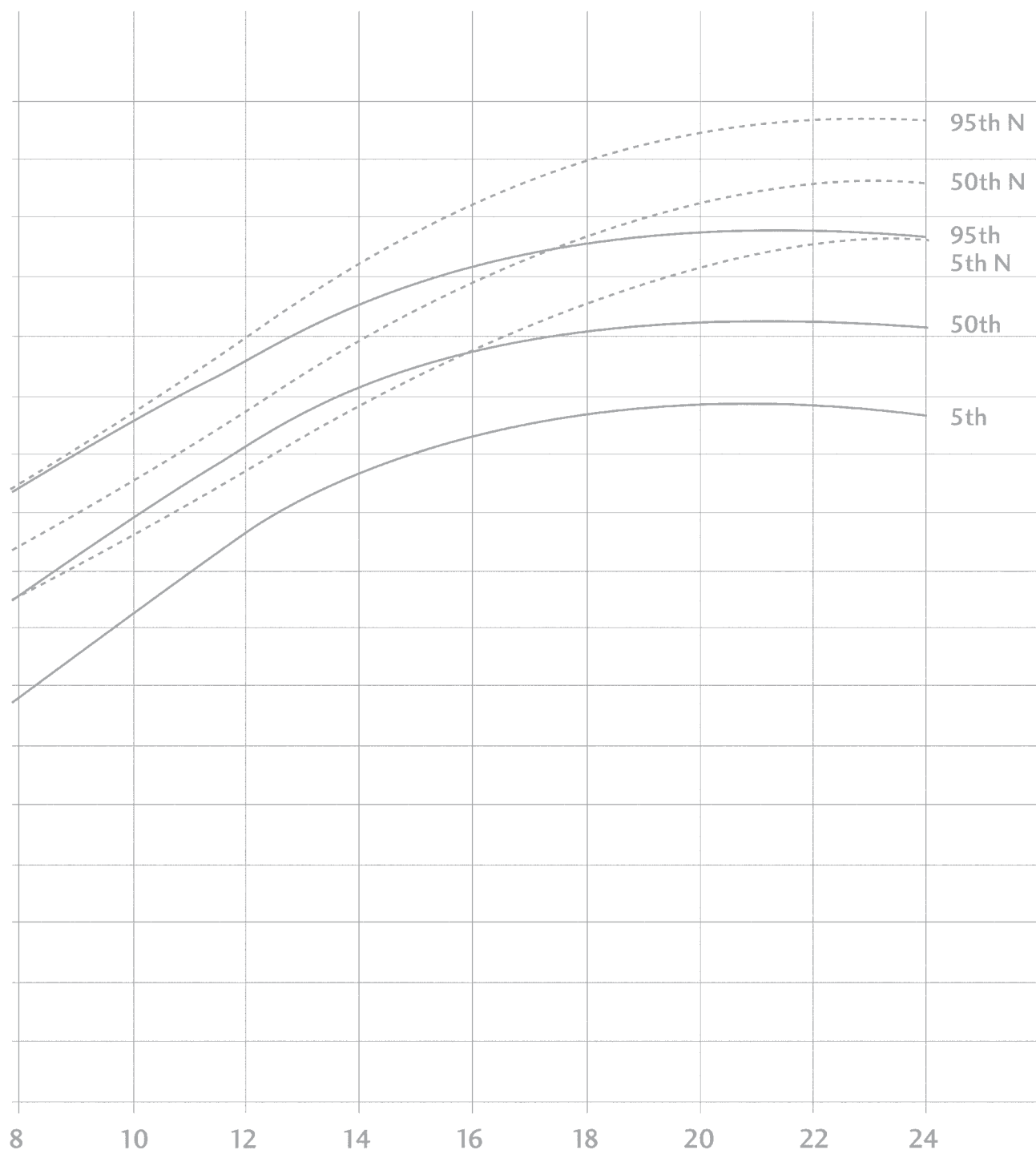
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## ABOUT THIS PUBLICATION

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**EDITOR** — The second edition of this publication was edited by **Don Goranson**, a recent retiree, who worked in the communications industry for 42 years. Goranson began his career in radio as a broadcast journalist; moved into newspapering and held the positions of reporter, assistant city editor and managing editor with a company that published both daily and weekly newspapers; and then rounded out his career in the Office of Communications of the Connecticut State Department of Education as Publications Unit Coordinator. Goranson served for seven years as vice president of PWSA (USA), for six years as a member of the Board of Directors of PWSA (USA), and is a former president of PWSA (USA)'s Connecticut Chapter. He served as both consulting editor and production coordinator of the first edition of *Growth Hormone and Prader-Willi Syndrome — A Reference for Families and Care Providers*, published in 2001. Married to Margaret Goranson, Don and Peg make their home in Bristol, Connecticut, and are the parents of David, a 42-year-old with Prader-Willi syndrome.

**DESIGNER** — Design and layout of this publication are the work of **Andrea Wadowski** of Burlington, Connecticut. Ms. Wadowski's graphic design was also featured in the 2001 edition of this publication.

**SPECIAL THANKS** — We wish to extend a heartfelt word of thanks to **Linda Keder** of Silver Spring, Maryland, a freelance editor and past editor of the PWSA (USA) national newsletter *The Gathered View*, who researched and wrote the first edition of this book in 2001. It is through Ms. Keder's efforts that the standards were established for this second edition.

**FUNDING** — Financial support for this project was provided through unrestricted educational grants from the RGK Foundation of Austin, Texas; and Eastside High School of Taylors, South Carolina. The grant from East Side High School comes from a student-sponsored Spirit Week fund-raising project that designated PWSA-USA as beneficiary.

**PHOTOS** — We wish to thank the unnamed families who generously shared photographs of their children and adults, and their experiences with growth hormone treatment.

**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.

## **ACKNOWLEDGMENTS**

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We are grateful to the following individuals, who made significant contributions of their time and expertise, both in content development and in service as professional reviewers.

**Moris Angulo, M.D.**, Director of Medical Genetics and Assistant Director of Pediatric Endocrinology at Winthrop University Hospital, Mineola, NY; and a member of the Clinical Advisory Board of PWSA (USA).

**Merlin G. Butler, M.D., Ph.D.**, Professor of Psychiatry, Behavioral Sciences and Pediatrics and a certified geneticist at Kansas University Medical Center, Kansas City, KS; and Chairperson of the Scientific Advisory Board of PWSA (USA).

**Kathryn Clark, RN, CS, MSN**, Pediatric Nurse Practitioner, Department of Pediatric Endocrinology, at the University of Michigan, Ann Arbor, MI.

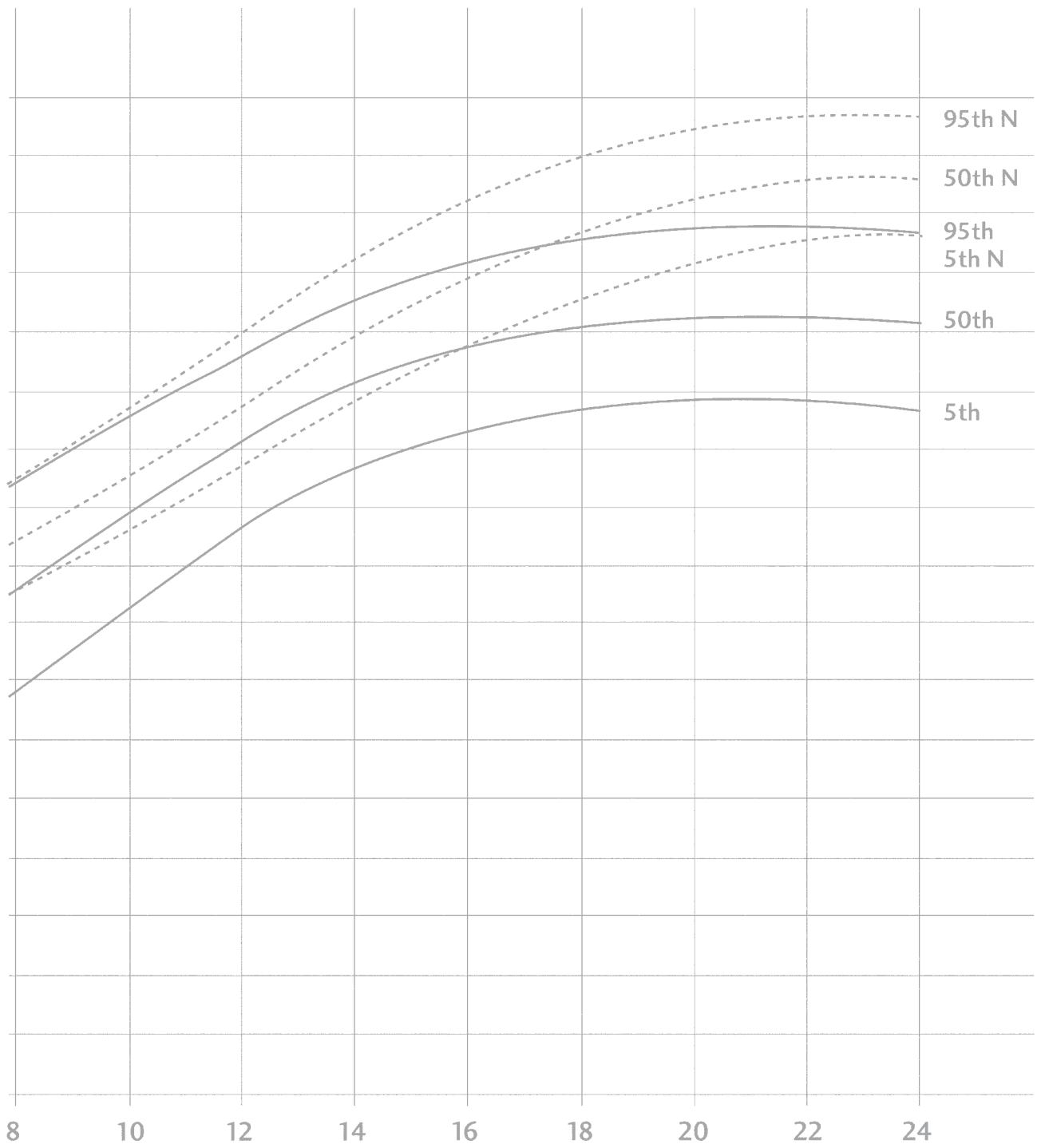
**Debra Hanley**, of Kingston, NY, parent of a daughter with Prader-Willi syndrome.

**Janalee Heinemann, MSW**, Director of Research and Medical Affairs of PWSA (USA) and Vice President of the International Prader-Willi Syndrome Organization (IPWSO).

**Jennifer Miller, M.D., M.S.**, endocrinologist and Assistant Professor, Division of Pediatric Endocrinology, University of Florida, Gainesville, FL; and a member of the Clinical Advisory Board of PWSA (USA).

**Harold J. P. van Bosse, M.D.**, surgeon, Department of Pediatric Orthopedic Surgery at Shriner's Hospital for Children, Philadelphia, PA.

**Barbara Y. Whitman, Ph.D.**, Professor of Pediatrics at Saint Louis University School of Medicine, St. Louis, MO; and a member of both the Scientific Advisory Board and Clinical Advisory Board of PWSA (USA).





## 1. INTRODUCTION AND HISTORY

---

*“Sean was unable to run for more than a few steps without experiencing pain, shortness of breath or without his little heart beating rapidly, nor could he hop, skip, jump, kick or climb anything with any agility. ... Most of this has changed rapidly after starting GH. ... Sean is now able to play on a Challenger Little League Baseball team, and he can run all the bases without a complaint. That is about the best part of all — Sean can play normally with other children. ... The additional strength helps in areas of self-care as well. ... I can’t begin to tell you how good it feels when your child accomplishes even one small thing other people take for granted.”*

*— Mother of a 5-year-old*

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**D**octors, researchers and parents continue to report many dramatic changes and positive outcomes from the use of human growth hormone (GH) in individuals of all ages with Prader-Willi syndrome (PWS). In the 10 years since the initial distribution of the First Edition of this publication in 2001, the use of GH has become standard care for those with PWS when prescribed by an experienced endocrinologist. In children, human GH can help with height, weight, body mass, strength and agility, and also may help with cognitive development. In addition, reports on the use of a low dose of human GH in the adult PWS population have shown positive results in the areas of bone strengthening and the promotion of leaner muscle mass and greater energy.

Prior to 1990, there were no scientific studies to show the use of human GH to be a good idea for children born with Prader-Willi syndrome. While some children with PWS did get treatment, others were denied treatment because it could not be proven that they had a growth hormone deficiency. 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. For those families the cost of the medication — and the promise of a better life for their child — was simply out of reach.

Pioneering some of the earliest reported work in this area were Dr. Moris Angulo, of Winthrop University Hospital in Mineola, New York, who currently serves on the Clinical Advisory Board of PWSA (USA), and Dr. Phillip Lee of Baylor University 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. Dr. Angulo, meanwhile, made a major 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. At the 1998 national conference of PWSA (USA), Dr. Martin Ritzen of Sweden reported impressive results from the first major study to compare children with PWS who were treated with growth hormone therapy with a similar group of children who were not treated. Not only did GH treatment increase height and growth rate dramatically, it was shown to reduce body fat and to increase muscle mass and bone size.

As more study results poured in, support mounted for GH treatment to be approved specifically for children with PWS. Doctors experienced in treating growth disorder in PWS began to agree that Prader-Willi syndrome causes a true deficiency of growth hormone secretion, probably originating in the hypothalamus portion of the brain. An international consensus statement signed by 21 endocrinologists worldwide was 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 for ... testing before treatment.”

By the time the July 2000 consensus statement was published, the U.S. Food and Drug Administration (FDA) had already taken action. In June 2000, the FDA approved an application from Pharmacia Corporation (since acquired by Pfizer), the makers of Genotropin® brand 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 deficiency testing.

Approximately 10 years later the FDA approved a second growth hormone treatment specifically for children with growth failure due to Prader-Willi syndrome. This latest product approval — in April 2010 — involves Omnitrope®, manufactured and distributed by Sandoz, Inc. Please review Appendix C for additional product information.

There is no longer any doubt that growth hormone treatment can improve the health and quality of life of children with PWS. The questions that remain are largely individual ones — how early to consider treatment, when there are good reasons to stop treatment or not to use GH in a particular child, and to what extent GH treatment will benefit an adult with PWS. PWSA (USA) does not endorse a specific age to begin growth hormone therapy, nor does the national organization recommend particular doses. Decisions regarding GH should be made by an experienced endocrinologist. Please see Appendix G for the full text of the June 2009 PWSA (USA) Clinical Advisory Board consensus statement on GH treatment.

Although human GH treatments do not decrease appetite, these therapies — together with early intervention — 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 can make decisions in the best interests of the child or adult with PWS.

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*“It has done wonders for his self-esteem. Little things, like opening the car door and buckling his seat belt, are no problems for him now.”*

*— Parent of a 6-year-old*

## 2. PRADER-WILLI SYNDROME AND GROWTH



This infant with extremely low muscle tone at 15 months (far left) shows an obvious increase in alertness and tone after three months of GH treatment.

### A Different Pattern of Growth

Children with Prader-Willi syndrome (PWS) grow and develop in ways that are different from other children. This is because their bodies don't make enough of certain hormones that are needed for normal growth. While there are individual variations, the following history is common for children with PWS who do not receive hormone treatment.

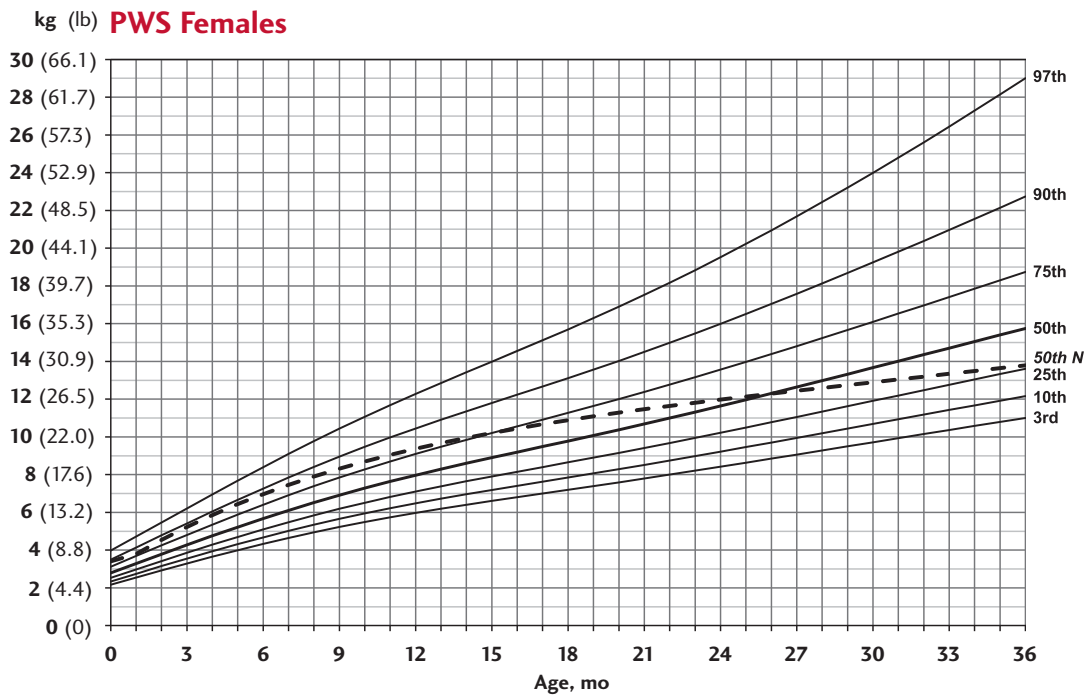
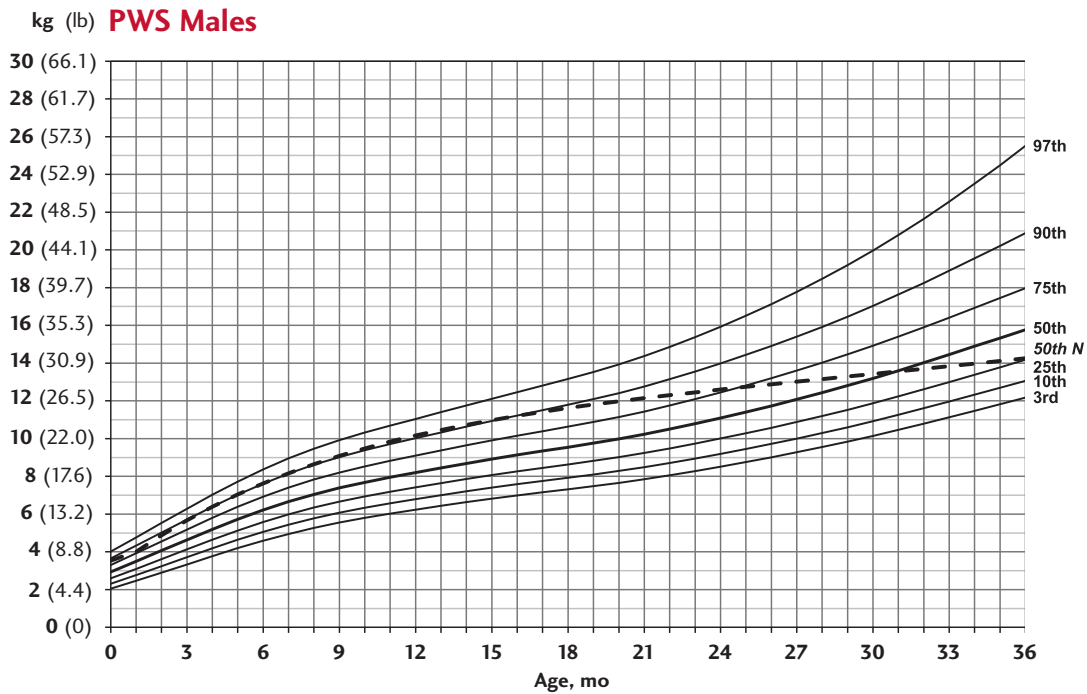
*In infancy and early childhood* — Most children with PWS are born with normal weight and length but are described as “floppy infants” because of their low muscle tone (hypotonia). Statistics show that 30 percent of these infants are born with low birth weights. Newborns typically have trouble feeding and gaining weight, and they often must be fed through a tube for a time in order to survive and grow. They gradually gain strength and eventually begin to reach their major milestones (sitting up, walking, etc.), although somewhat later than other children their age. As young children with PWS continue to develop, their body fat seems to grow at a much greater rate than their muscle and height. Although they are eating well, they 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.

A group of 10 U.S. researchers, six of whom serve on either the Scientific Advisory Board or the Clinical Advisory Board of PWSA (USA), published five sets of standardized growth curves for infant boys and girls with PWS in April 2011. These data and growth curves, representing 186 non growth hormone-treated white infants between 0 and 36 months of age, were published in *Pediatrics*, the official journal of the American Academy of Pediatrics, and are reprinted with permission on pages 10-14 of this publication.

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 released in 2003 by the Centers for Disease Control and Prevention. Of additional interest, 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.”

PWSA (USA) Scientific Advisory Board Chairperson Merlin G. Butler, M.D., Ph.D., of the Kansas University Medical Center, offers the following context-setting statement in behalf of the group of researchers: “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.”

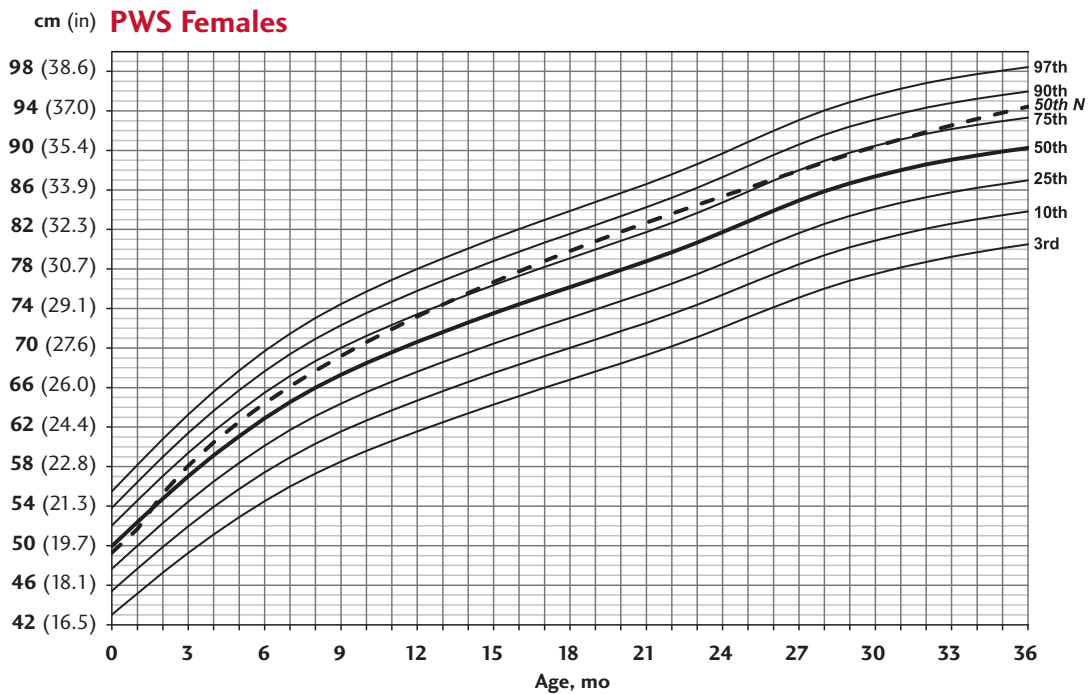
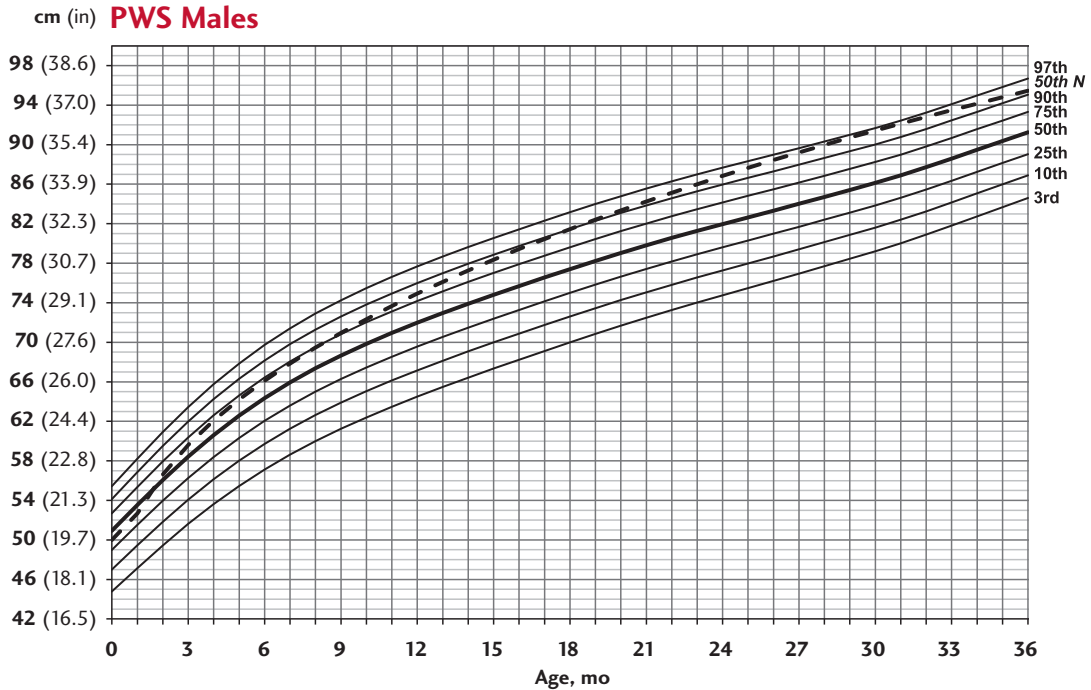
## WEIGHT OF INFANTS WITH PWS COMPARED WITH NORMAL WEIGHT FOR AGE



**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.

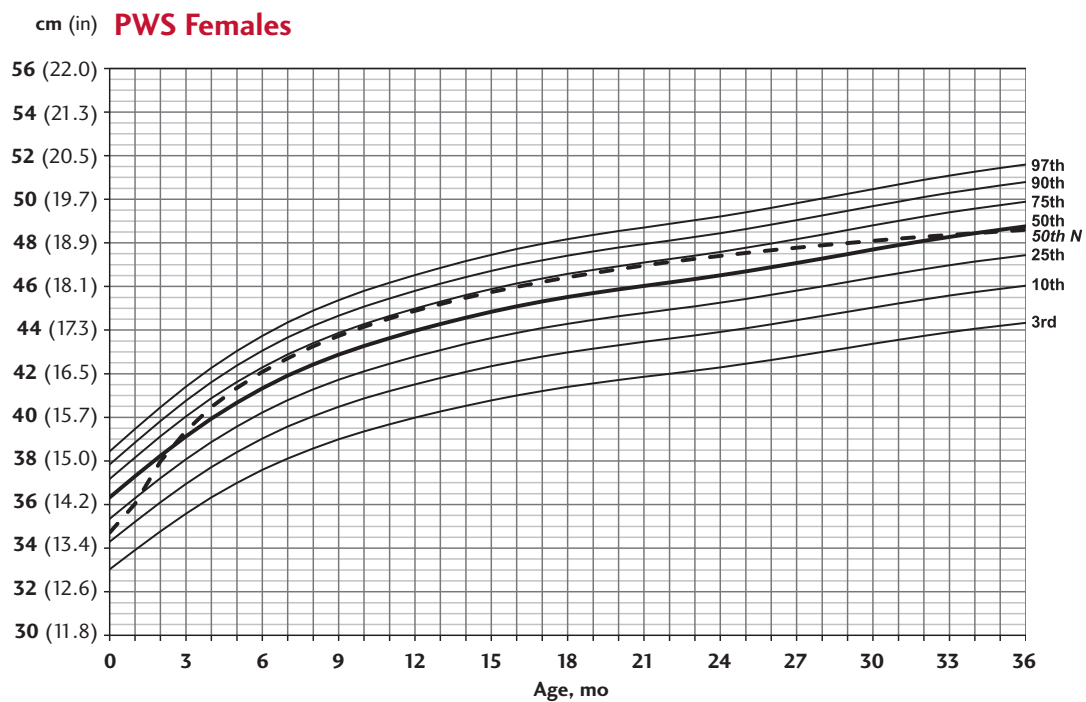
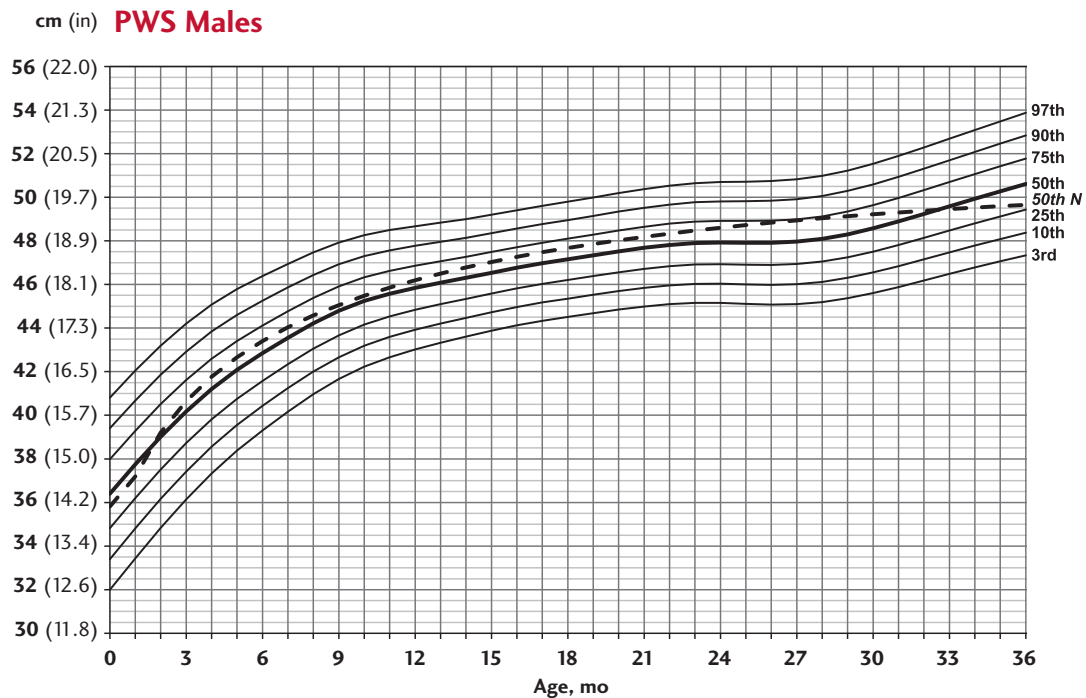
## LENGTH OF INFANTS WITH PWS COMPARED WITH NORMAL LENGTH FOR AGE



**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

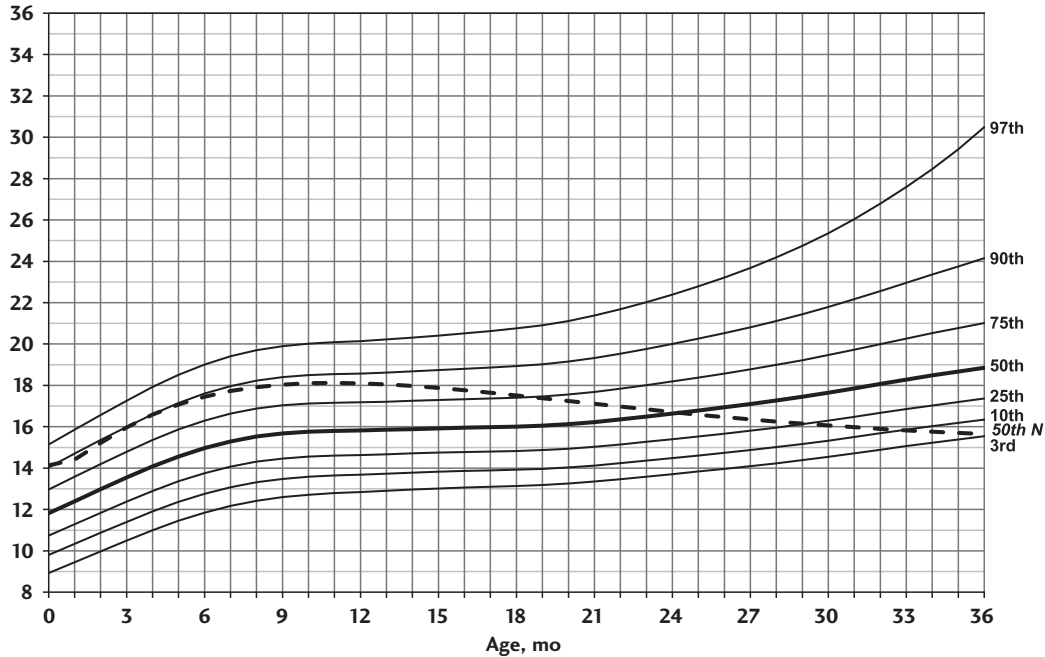


**Standardized curves for head circumference of male (upper) and female (lower) infants with PWS (solid lines) and normative 50th percentile (broken line).**

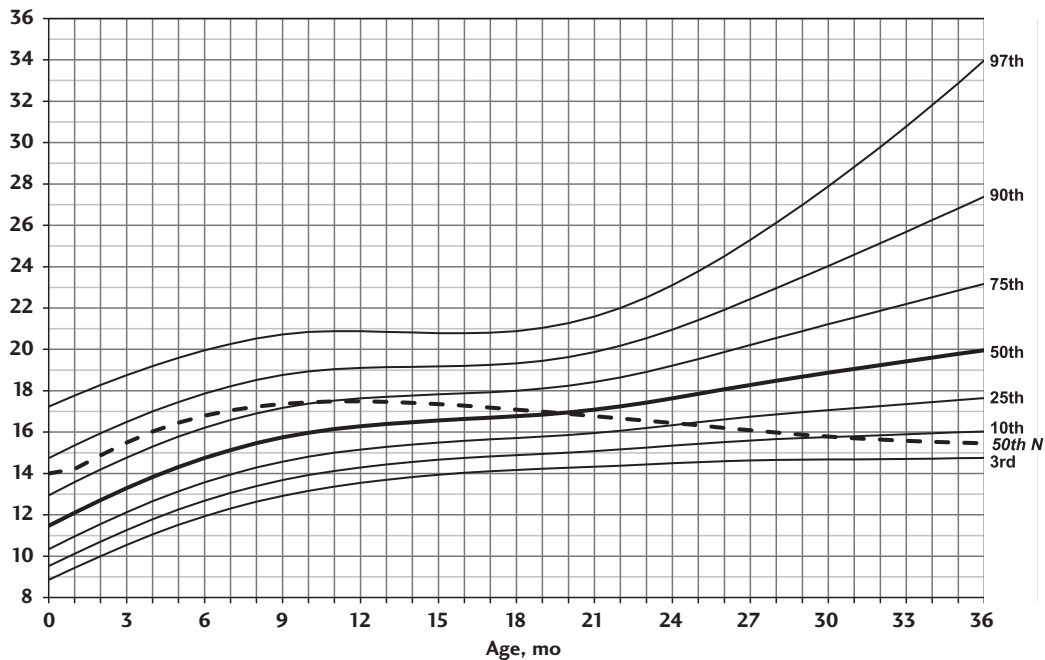
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## BMI OF INFANTS WITH PWS COMPARED WITH NORMAL BMI FOR AGE

kg/m<sup>2</sup> **PWS Males**



kg/m<sup>2</sup> **PWS Females**



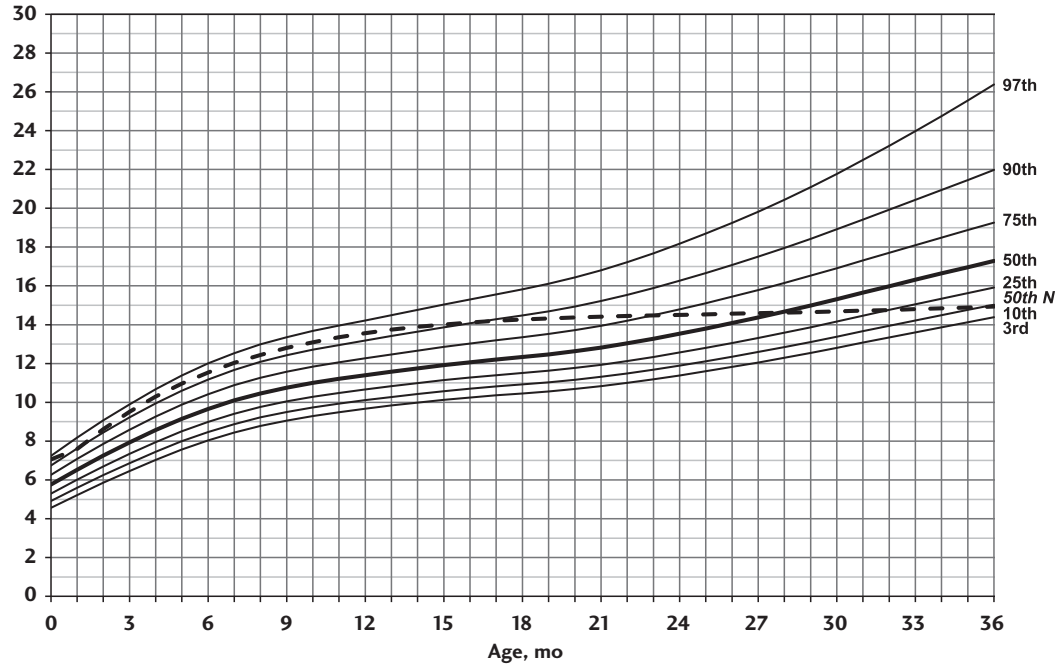
**Standardized curves for BMI of male (upper) and female (lower) infants with PWS (solid lines) and normative 50th percentile (broken line).**

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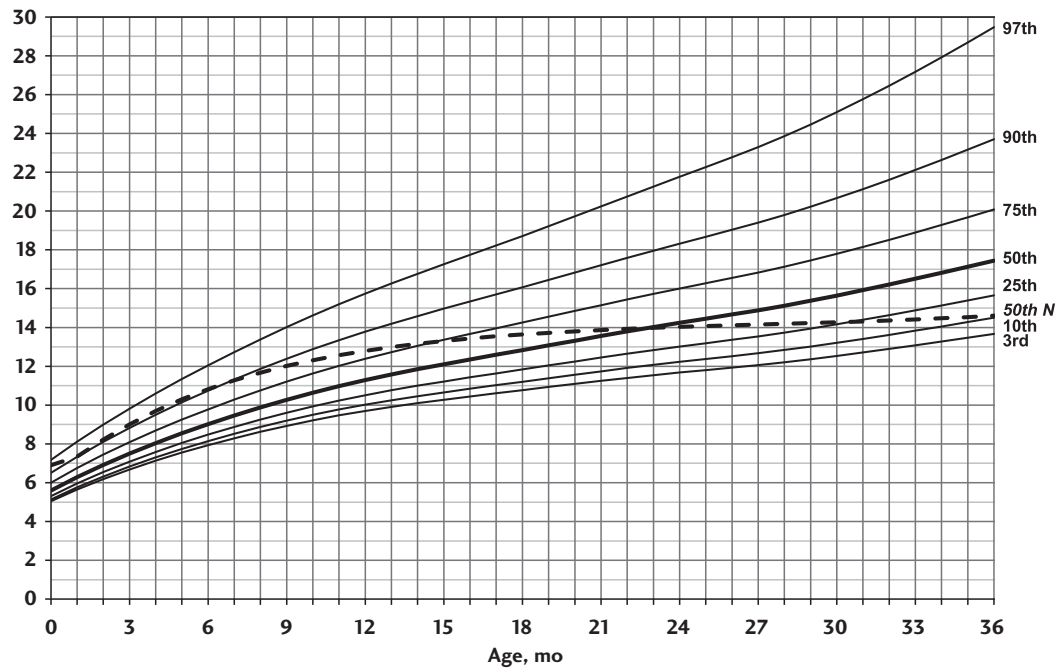


## WEIGHT/LENGTH OF INFANTS WITH PWS COMPARED WITH NORMAL WEIGHT/LENGTH FOR AGE

**kg/m<sup>2</sup> PWS Males**



**kg/m<sup>2</sup> PWS Females**



**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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*In later childhood and beyond* — Through the school-age years, a common physical profile usually becomes apparent in the child with PWS who has not received the benefits of human growth hormone therapy. He or she is likely to have short stature (compared with that of classmates and other family members), small hands and feet, poor muscle development and 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 children 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 all the bodily changes that occur with sexual development. 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. This means that adults with PWS are shorter than nearly all other adults. (See height charts on page 18.)

**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?

Researchers strongly suspect that the part of the brain called 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 regulates appetite, metabolism, body temperature, mood and other functions that we know are affected in people with PWS. It is likely that one or more of the genes that are missing (or not functioning) in people with PWS supply essential instructions to this part of the brain.

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. 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 makes and releases many hormones. Among these are growth hormone (GH) and the hormones for sexual development and reproduction (LH and FSH). If the pituitary does not make or release enough of these hormones, then the organs that depend on them cannot do their jobs.



This 3-year-old was below the 5th percentile in height when she started GH (above). After two and a half years of treatment (below), she had grown about nine inches and reached the 45th percentile for her age. Her skinfold measurements showed a decline in body fat from the 75th percentile to the 35th percentile.



## How Growth Hormone Works

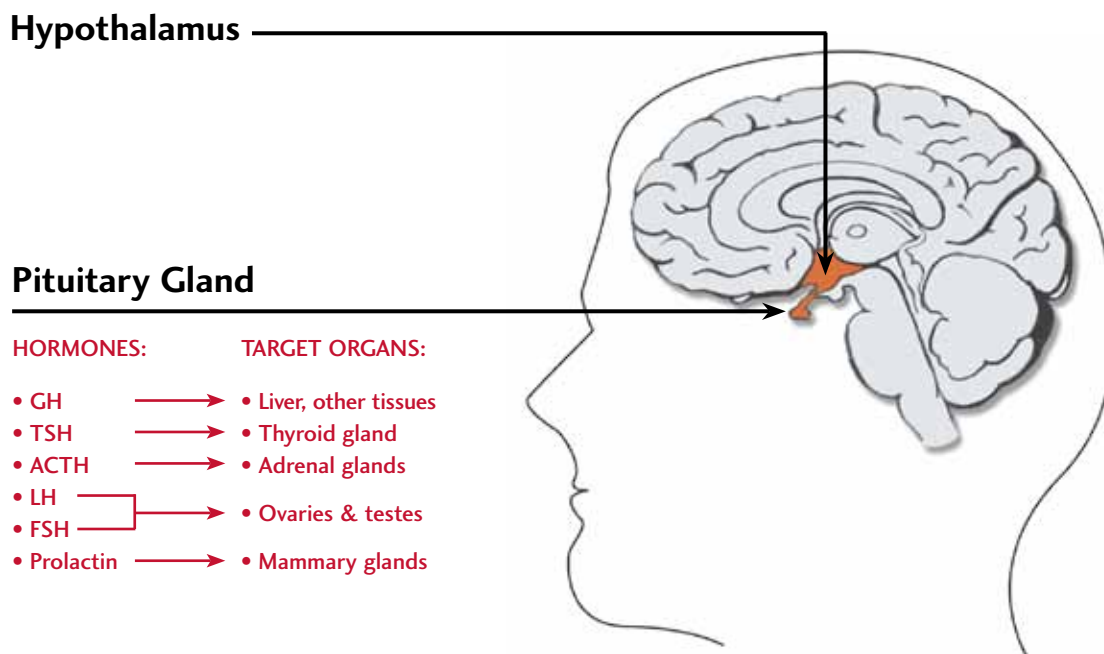
The growth hormone process begins when the hypothalamus sends a chemical messenger called growth hormone releasing hormone (GHRH) to the pituitary gland. This signals the pituitary to release growth hormone, which it does in small spurts throughout the day, but especially during the first hours of sleep.

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. It signals the liver to make and release the substances that do — the insulin-like growth factors. The main one of these is a protein called insulin-like growth factor-I (one), or IGF-I. It is IGF-I that stimulates new cell growth in the cartilage near the ends of the skeletal bones (called the epiphyses) and in the muscle tissues.

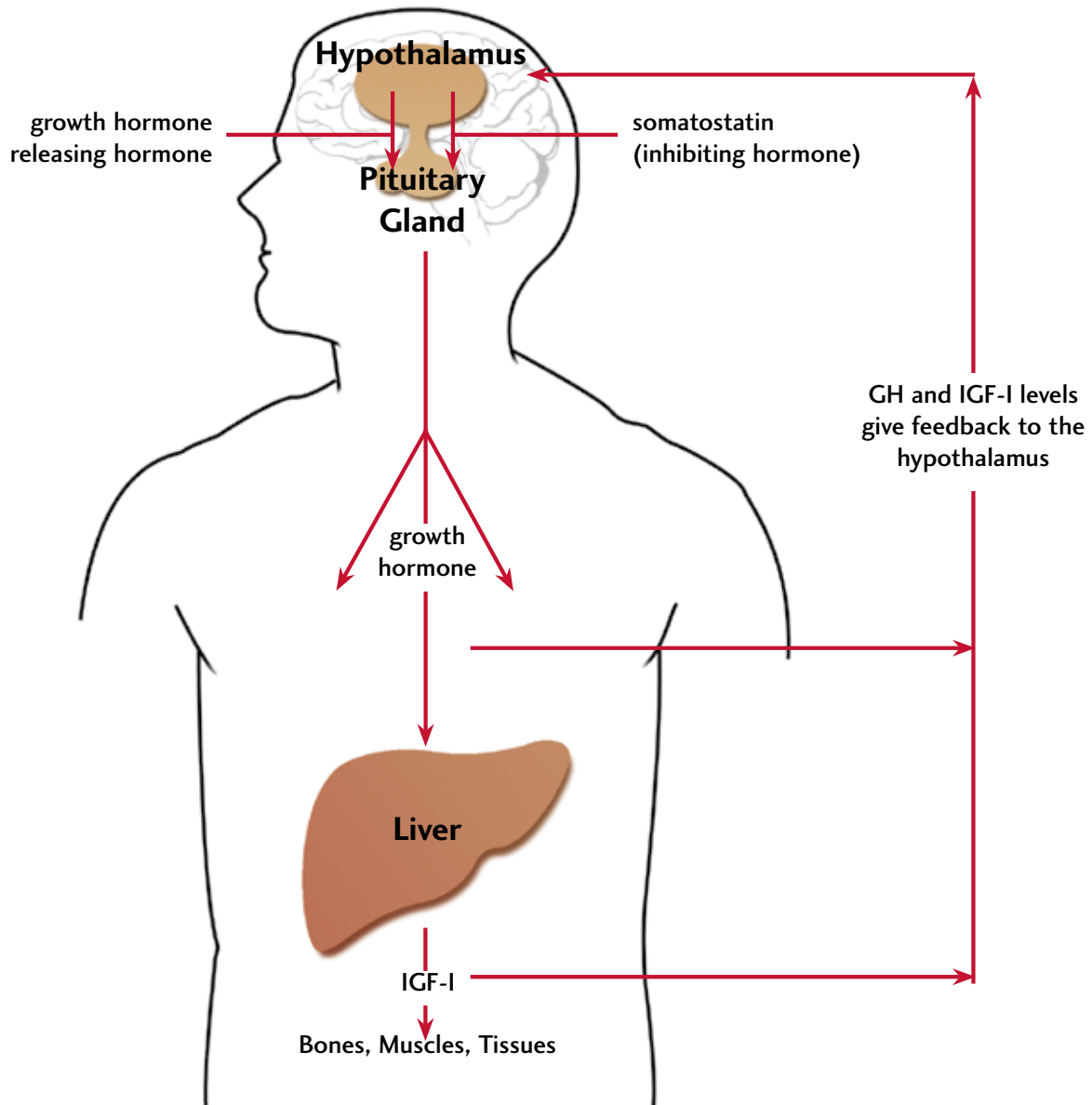
The body's growth system also has checks and balances. For example, when there is a high level of GH or IGF-I in the system, the hypothalamus receives the message and produces a different hormone called somatostatin, which tells the pituitary to stop releasing GH into the bloodstream.

## Growth Problems and Treatment

Growth can be adversely affected if there is a problem at any level of the process: in the work of hypothalamus, the pituitary gland, the liver or the feedback system to the hypothalamus. When the pituitary gland doesn't make or release enough growth hormone, or when the growth hormone that is made is not effective in the body,



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.

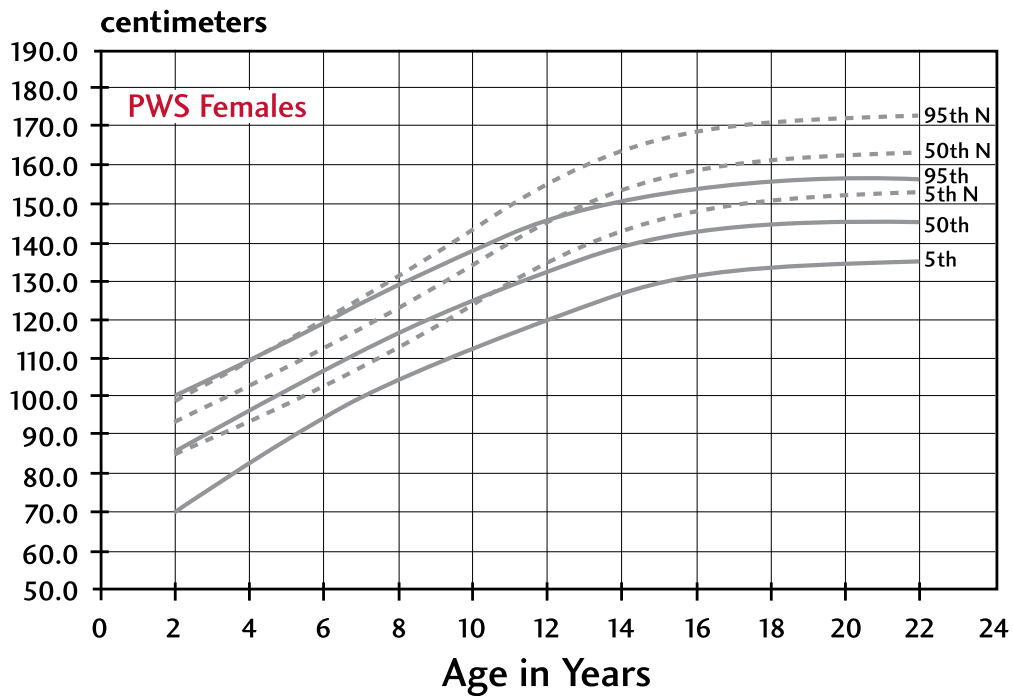
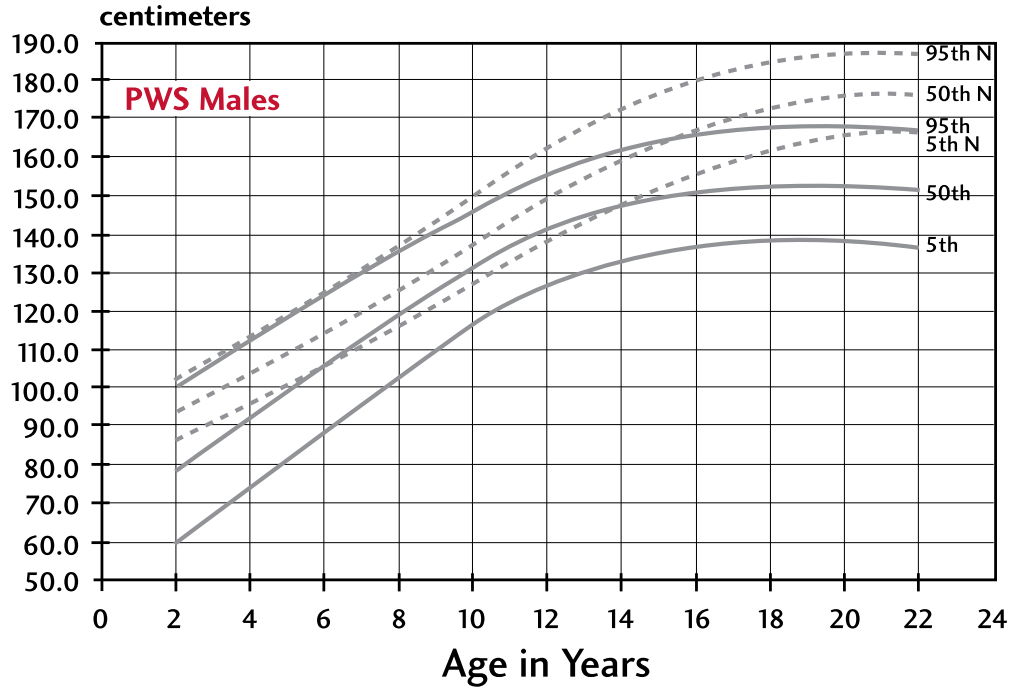


signs of growth hormone deficiency (GHD) will begin to appear. These include many of the growth-related characteristics seen in people with PWS — short stature and slow growth rate, poor muscle development, increase in central body fat, reduced activity level, etc.

Growth also is affected by other parts of the endocrine system, such as the thyroid and reproductive hormones (which might also be deficient), as well as by an individual's diet, sleep, exercise level, etc. The human growth process and regulation is very complex, and 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 synthetic growth hormone 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. Pharmaceutical representatives report that a noninjectable form of human GH is not likely to become available in the foreseeable future.

## 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 healthy individuals (broken line). (M.G. Butler and F.J. Meaney)  
Reproduced by permission of *Pediatrics*, Vol. 88, p. 853-860, copyright 1991.

GH therapy became widely available in 1985, when the first manufactured form of growth hormone was approved for sale in the United States. GH has since been proven safe and effective in correcting problems in growth and body regulation caused by GH deficiency. 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

For a 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. Testing for GHD has been a controversial issue in itself, however, because the body's level of GH is difficult to measure and may show different results on different tests.

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. However, while the widely accepted tests for GH can measure deficiency when it is severe, they may miss the cases where it is a functional or evolving deficiency. That is why GH deficiency testing is no longer required for children with 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 in the infant, child or adult with PWS. The Appendix includes additional information and resources regarding Prader-Willi syndrome and growth hormone, including the text of the 2009 PWSA (USA) Clinical Advisory Board consensus statement on PWS and growth hormone, announcement of the two FDA approvals of GH treatment products Genotropin® and Omnitrope® specifically for PWS, summaries of GH clinical trials in children and adults with PWS, and a glossary of terms.

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*“The most important benefit is self-esteem. She is very aware that she is bigger now and growing. It has been a positive social factor in her grade one integration and special-needs class.”*

*— Parent of a 6-year-old*

---

*“Growth hormone makes a huge difference in Ian’s quality of life. ... He continues to grow and improve his strength, alertness, level of activity and endurance.”*

*— Parent of a 4-year-old*

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



Reports from a number of research groups around the world have confirmed what was suspected in the late 1980s: growth hormone treatment (GHT) offers many benefits to children and adults with Prader-Willi syndrome (PWS). Studies on GHT use in infants and adults have been positive, but answers are still evolving. How young do you start GHT? Is there an age when you stop GHT? These are just two of the questions with no clear answers to date, but you are invited to contact PWSA (USA) for updates.

Information in this section addresses the benefits and potential side effects of GHT. Results of some of the major studies are outlined in greater detail in Appendix E.

#### BENEFITS OF GH TREATMENT

##### Measured Improvements

The following physical changes have been documented in various research studies, and the most dramatic results are reported in the first year of GH treatment. Studies in the United States and other countries followed children beyond one year of treatment and reported some additional improvements.

- **Increased height and growth rate** — Treated children grow in height at double or more the rates 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 starting age of treatment, a child's final height can be closer to that of others in the family.
- **Increase of hand and foot sizes to normal proportions** — GH treatment enables hand and foot sizes to catch up with height growth in just one year. Without GH treatment, people with PWS typically have small hands and feet for their body size, which can affect motor skills.
- **Little change in body fat** — Excess fat is characteristic of PWS, but data from a recent study shows that there was no real difference in the fat levels of children with PWS who had received growth hormone treatment for a period of six years. This was especially true for children whose parents were unable to provide proper structure. According to Barbara Y. Whitman, Ph.D., professor of pediatrics at Saint Louis University School of Medicine, "It was disappointing that there wasn't that much difference in accumulation or percentage of fat, but there was significantly improved muscle mass and better bone density and height."
- **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.
- **Increase in muscle development** — Improvements have been shown in measured size of muscles and in muscle as a percent of body weight. Muscle growth does not quite reach normal levels, although it is significantly improved. Young, underweight children in one study gained weight because of the increased muscle.



- **Improved respiratory function** — GH-treated children can breathe better, due to stronger respiratory muscles and improved response to build-up of carbon dioxide (CO<sub>2</sub>).
- **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 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.
- **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.
- **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** — One study of children with PWS who received growth hormone treatments from infancy for a period of six years shows a much more normal head circumference. This result may serve as an index for better brain growth.



This young man clearly illustrates the consequences of the growth disorder in Prader-Willi syndrome (two photos on left) and the correction that is possible with GH treatment (two photos on right). As shown on his growth chart on page 23, this boy was able to achieve the 50th percentile for both height and weight after just two years of GH therapy.

Photos reprinted by permission of *The Endocrinologist*, Vol. 10, No. 4, Suppl. 1, p. 48S.

## 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 the U.S. growth hormone study suggests that GH treatment may have positive effects on depression, obsessive-compulsive 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.

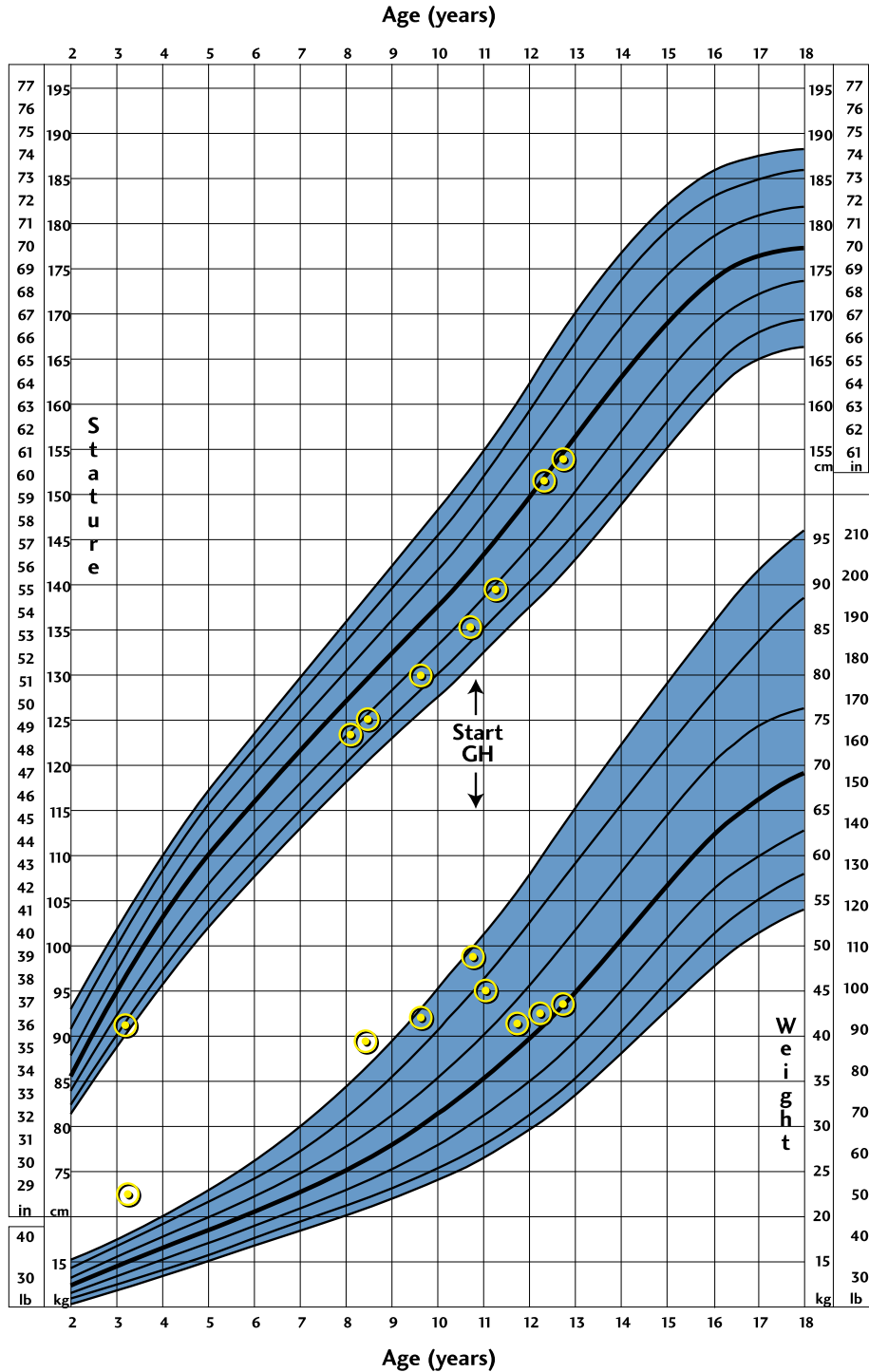
## AREAS OF NO CHANGE

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

- **I.Q. (intelligence quotient)**  
Although some parents say their children seem more focused or alert with GH treatment, none of the studies measured changes in I.Q. or suggested that GH treatment might affect I.Q.
- **Behavioral problems such as temper outbursts**  
Because behavior is such a concern in PWS, the 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.
- **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**  
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.



## 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 pictured on page 21 at various ages. 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.

## SIDE EFFECTS

**EDITOR'S NOTE:** Please review **Appendix G — PWSA (USA) 2009 Consensus Statement — and Appendix I — PWSA (USA) Precautions Statement — for additional comprehensive information on possible side effects and standard warnings about growth hormone treatments.**

As with any medication, GH therapy may cause undesirable side effects in some cases. The risks and benefits of GH treatment, therefore, should be thoroughly discussed with the child's or adult's physicians **prior** to making a decision to proceed. 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 the studies of children with PWS found no widespread side effects of GH treatment, they noted some individual experiences that required attention. These reactions to GH treatment are rare, but they do sometimes occur:

- **Headaches**  
Some children 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 the initiation of GH treatment. The headaches sometimes have stopped on their own, but in some cases it was necessary to lower the child's dosage and raise it more gradually. Rarely, headaches can be severe and may be accompanied by vomiting and vision disturbances due to fluid pressure in the brain. This condition may be called intracranial hypertension or pseudotumor cerebri. Although the symptoms seem very serious, they go away when GH treatment is stopped. The child 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. This problem can 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 needed to use and store carbohydrates and reduce glucose levels in the blood. 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. Children with PWS and GH deficiency should be monitored carefully for signs and symptoms of glucose intolerance during GH treatment, particularly if they are massively obese or have a family history of diabetes mellitus. If diabetes mellitus occurs while on GH therapy, the GH treatment should be stopped. If restarted, the GH dose should be substantially reduced.
- **Decreased levels of thyroid hormone (thyroxine)**  
Some children with PWS developed thyroid deficiency after they started GH treatment and required 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, otolaryngologist

and gastroenterologist before and shortly after beginning GH treatments. (Please See Appendix J — Recommendations for Evaluation of Breathing Abnormalities Associated with Sleep in PWS.)

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

Children with PWS have an increased risk for spinal curvature abnormalities, including scoliosis and kyphosis, believed to be caused by weak muscles and loose joints. Although rapid growth can cause a scoliosis curve to worsen, PWS studies found no significant difference in curve progression between the children with scoliosis who were treated with GH and those not receiving GH treatment. Several children in the studies, however, did require treatment of their scoliosis — either a back brace or surgery, depending on their degree of curve. Detection and monitoring of scoliosis are important for all children with PWS, whether or not they are receiving growth hormone treatments. Decisions to initiate or continue GH treatments in a child 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 caused by too much growth hormone in the body, a rare condition usually caused by a tumor on the pituitary gland. This condition causes distorted growth of the brow, jaw and other body parts, as well as damage to internal organs and processes. Acromegaly is a 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 occurred in any of the PWS research studies, and 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 a child has an active tumor or cancer, growth hormone therapy is not advisable. A child who once 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 child’s physicians. There is no evidence that GH causes cancer.

**Slipped-capital femoral epiphysis (SCFE)** — This term describes a condition almost like a break in the top of the thigh bone (femur). The cartilage in the area of bone growth (called the epiphyseal plate or growth plate) slips from the top of the femur for reasons not well understood. 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.

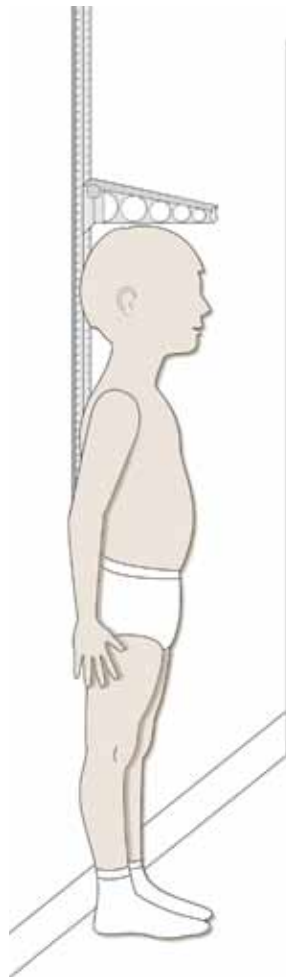
## 4. WHAT IS INVOLVED IN GROWTH HORMONE TREATMENT?

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?

To decide whether a child or adult needs to be treated with growth hormone, a family normally sees a specialist called an endocrinologist. Endocrinologists are doctors who specialize in the body's hormones, including growth hormone, sex hormones, insulin, thyroid, etc. There are pediatric endocrinologists, who specialize in treating children, and adult endocrinologists, who treat adults and possibly adolescents. Since there are a number of medical issues in Prader-Willi syndrome (PWS) 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.

If a family has health insurance benefits through an HMO (health maintenance organization) or other type of managed care plan, 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. The child's growth may need to be monitored for a period of time before the endocrinologist can determine whether there is "growth failure due to Prader-Willi syndrome." (In June 2000, the FDA approved use of GH treatment for this condition.)

Endocrinologists take careful measurements of a child's height using a wall-mounted ruler or a special measuring board for children under 2- to 3 years old. Typically the child is measured several times at the same visit to ensure accuracy. Results are recorded on standard growth charts to determine how the child's height compares with others of the same age. 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 usually are significantly shorter than their peers or shorter than would be expected for their family. (Note: Standard growth charts for various ages are available on the U.S. Centers for Disease Control's Web site: [www.cdc.gov/growthcharts/](http://www.cdc.gov/growthcharts/).)

Other tests that might be done as part of a GH evaluation include a blood test to check the level of thyroid hormone (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 (often corrected by removing the tonsils and adenoids) and central sleep apnea,

or hypoventilation. The hand x-ray is compared with a set of standard x-rays for different ages and can tell the doctor how much bone growth potential the child has left. (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 affecting children with PWS, adults are required to undergo diagnostic blood studies to formally establish growth hormone deficiency. Although linear bone growth would no longer be a concern, reports on the use of a low dose of GH in the adult PWS population have shown positive results in the areas of bone strengthening and in the promotion of leaner muscle mass and greater energy.

### 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 (McCandless, et al., 2011). 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. GH treatment has been safely used in infants with growth hormone deficiency for many years. Studies confirm that GH treatment can improve muscle and motor development in infants with PWS.

Growth failure does not always mean that a child must drop below normal range for height or length but, rather, that his or her own pattern of growth fails to keep pace with normal growth speeds. Thus, a shorter child might grow at a normal speed and be considered to have normal growth, and a taller child with poor growth would be of greater concern.



A 5-year-old with PWS (at left in both photos) is much shorter than her 3-year-old sister (top photo), but is beginning to close the gap after one and a half years of GH treatment (bottom photo).





## 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.

The Clinical Advisory Board of PWSA (USA), in its June 2009 consensus statement (see Appendix G), cautions that children with PWS have “an increased prevalence of respiratory dysfunction.” A sleep study is recommended before the start of GH treatment in all infants, children and adults with PWS, with a follow-up study six to eight weeks later. If sleep apnea worsens, it is recommended that it be managed by the appropriate standards of care (American Academy of Pediatrics, 2002), including seeing an 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 study improves.

## How is GH administered?

One of the challenges of growth hormone treatment is that the patient’s family or caregivers must learn to give injections at home. Like insulin, GH is a protein (not a steroid) hormone that must be injected through the skin in order to reach the bloodstream and be effective in the body. Also, like insulin shots, the GH injections are usually 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 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 nightly or six times a week by the parent, caregiver or the child 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. Over the years, experience has shown that daily shots gave more effective results than injections only three or four times a week. Families also generally find it easier to make the injection part of the regular bedtime routine rather than to alternate injection days.

## 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 (see Appendix C).

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 injection under the supervision of a nurse. The growth hormone supplier also might provide an instructional video

for 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 (See Appendix C). 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 GH products now in use is somatropin, rDNA origin, for injection. The "rDNA" (recombinant DNA) means 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 methods 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 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.

FDA approval of two GH products for Prader-Willi syndrome (Genotropin® and Omnitrope®) has opened the door for doctors to prescribe all equivalent products for that use as well. 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. (See Appendix C for information on the various GH manufacturers and their products.)

## How is a child's dose of GH determined?

There are some commonly accepted dosage ranges for GH treatment in infants, children and adults, but endocrinologists may vary in choosing a starting dose. In the United States, individual dosages of GH are expressed in milligrams (mg) of the protein powder form of GH to be given, either per injection or per week.

For infants with Prader-Willi syndrome, the dosing is based on body surface area. The typical starting dose is 1 mg/m<sup>2</sup> per day. In older children, beginning doses are typically calculated based on weight alone, or ideal body weight if the child is significantly overweight. Most endocrinologists adjust doses in older children after monitoring growth velocity, weight and IGF-1 (Insulin-like Growth Factor-1) level. The largest dosage is given



At the time of diagnosis, this 1-year-old girl with Prader-Willi syndrome showed classic low muscle tone and excess body fat. After nearly three years of growth hormone treatment, starting at age 9, this girl's height and weight are closer to normal and her moderate scoliosis has been improved with brace-wearing and growth.



at the time of puberty, when children normally have their last big growth spurt. For adults, there are standardized dosing regimens for beginning GH treatments. The adult dosage then is subsequently titrated based on IGF-1 levels. (See Appendix G for additional information on 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 on GH treatment. At each checkup, the child will be carefully measured for growth and generally examined. Periodically, the follow-up visits may also involve tests for:

- thyroid 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); 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 child responds to GH treatment. Since calorie needs may change with increased growth, a consultation with a dietitian should be considered to ensure that the child is receiving proper nutrition. Any specialists that the child normally sees on a regular basis (e.g., eye doctor, dentist, orthopedist, physical therapist, etc.) should be made aware that the child 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 child in their area of specialty.

### How does scoliosis affect GH treatment?

Orthopedic specialists recommend that children be monitored for scoliosis as soon as they begin sitting. Children with diagnosed scoliosis can be treated with GH if an orthopedic surgeon is involved to monitor the child's curve frequently, and to treat any significant curve progression that requires bracing or surgery. Frequent back x-rays (as



often as every 4 to 6 months) may be necessary. Back curves measuring between 20 and 40 degrees are often successfully treated with a brace, but curves that advance to more than 40 degrees in a growing child generally require major surgery to stabilize the spine. Unfortunately, doctors are unable to predict which mild curves will progress with growth.

Treatment with GH also can have positive effects on the spine—strengthening back muscles and increasing bone density — which may improve the child’s outlook for scoliosis treatment. The endocrinologist and orthopedic specialist should coordinate care and keep each other informed of changes in the child’s condition or treatment.

While scoliosis is a major concern, the prevalence of scoliosis has been found to be the same in individuals with PWS regardless of GH treatment. Therefore, scoliosis should no longer be considered a contraindication for GH treatment.

### When does GH treatment end?

Treatment at childhood dosage levels of GH stops when the growth plates near the ends of the bones have closed. This means that the cartilage where growth occurs has all solidified into bone, and there is no more growth potential. In the past, children always ended their GH treatment at that point. 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.

Studies of adults with GHD have found that a low dose of GH can help these problems, leading the FDA in 1996 to approve use of GH for adults with growth hormone deficiency. Adults with PWS may need to have



Changes in body composition are obvious in this 3-year-old girl with Prader-Willi syndrome, photographed before (left) and three months after starting growth hormone treatment.

documented growth hormone deficiency in order to be treated with growth hormone. (The FDA approval for GH use in Prader-Willi syndrome only covers children.) 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). 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 important for families to read carefully their insurance policies and any “riders” that amend the policies to find out what prescription drug benefits are provided, what is required to obtain them for GH treatment, and what limits have been set on either prescription drug benefits or 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.

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*“Seems to be displaying more ‘mature’ behavior. More accepting of chores. ... Almost no more nail biting or picking at skin around fingernails.”*

*— Parent of a 9-year-old*

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*“Food is a lot more manageable. If we have a high-calorie [meal] she doesn’t immediately gain 2 lbs. If she gains weight, she can lose it.”*

*— Parent of a 4-year-old*

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 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](http://www.cms.gov).)

Realizing that health insurance coverage is a major issue that may prevent a child from getting needed treatment, growth hormone manufacturers may supply the medication at no cost or at reduced cost for a period of time to eligible patients who are working to obtain insurance coverage or other funding. (See Appendix C for the patient assistance programs of the various GH manufacturing companies.)

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*“Sarah’s muscle strength and ability to run, jump, catch, etc., have improved dramatically since starting growth hormone treatment.”*

*— Parent of a 6-year-old*

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*“After only two months she sleeps less and is more active. ... Started standing on her own and trying to take steps, seems more brave.”*

*— Parent of a 20-month-old*

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

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### How can I find an endocrinologist to assess my child?

Ask your child's pediatrician or internist 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 also. Call several doctors and ask about having your child with PWS assessed for GH treatment. 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 1-800-926-4797 for information to share with your endocrinologist.

### 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. The FDA approved Pharmacia Corporation's (now Pfizer) application to market and promote their existing GH product, Genotropin®, for "long-term treatment of pediatric patients who have growth failure due to Prader-Willi syndrome." In April 2010, the FDA approved a second growth hormone treatment specifically for children with growth failure due to PWS. This latest product approval involves Omnitrope®, manufactured by Sandoz, Inc. 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 F.

### What happens if my child stops GH treatment?

People who stop taking growth hormone will not lose their height gains, but they will gradually lose the other physical benefits that GH produces, i.e., muscle development, fat reduction, increased energy level, etc., 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 child's doctor.

### 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, they are not effective for the needs of children with PWS. 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.

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*“I feel growth hormone has helped Kristine progress a great deal. ... She moves around better than before, is talking more, communicates a great deal more.”*

*— Parent of a 2-year-old*

## PARENT 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!”

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*“Her behavior has definitely changed — some good, some bad — but it is a more normal behavior.”*

*— Parent of a 6-year-old*

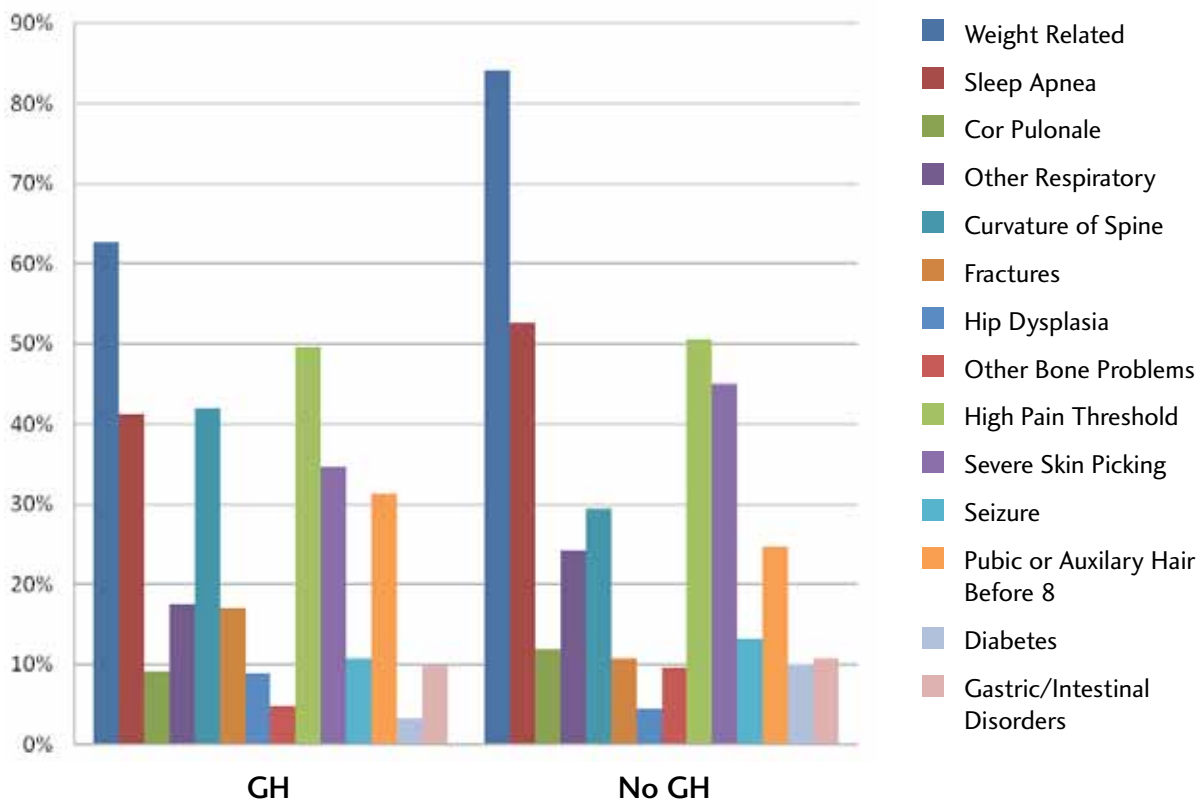


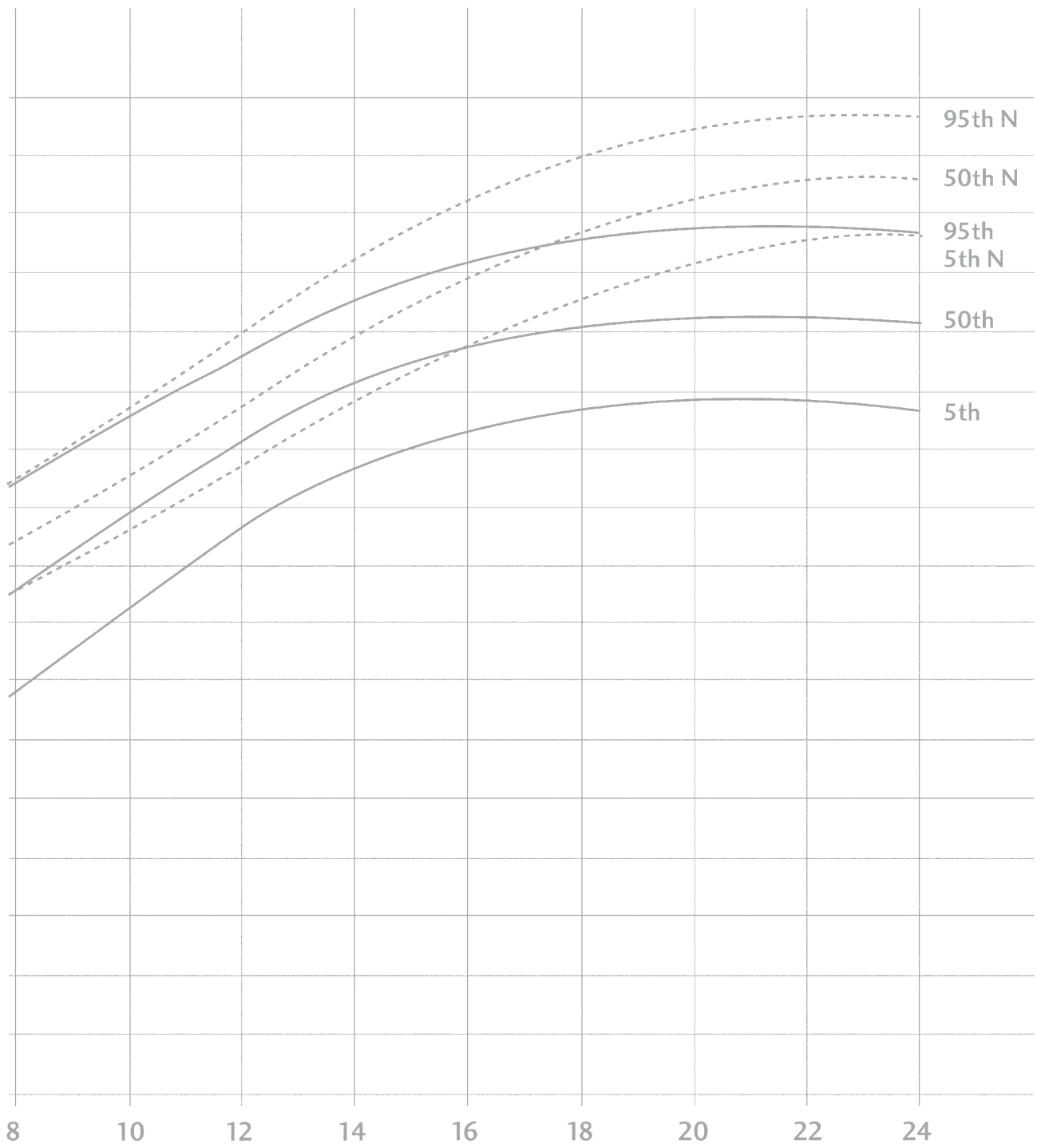
## SURVEY DATA

Beginning in October 2004, PWSA (USA) has been collecting data from the parents and/or guardians of children with Prader-Willi syndrome (PWS) who have been receiving growth hormone treatments. The on-line survey is available on the PWSA (USA) website; the quick link is [www.pwsausa.org/population](http://www.pwsausa.org/population) found under “Support: Registration of People with Prader-Willi Syndrome”.

The detailed chart of collected data, below, reflects information from 643 of the 1,868 parents and/or guardians who had responded to the survey up to April 2011. Of the 643 respondents who have children with PWS between the ages of 6 and 18, 393 reported having children who had been receiving growth hormone treatments either continuously, or for varying periods of time. The accompanying survey chart details the relationships in more than a dozen medical categories of those who had both received and NOT received growth hormone treatments.

### PWS AGES 6 TO 18 WITH AND WITHOUT GROWTH HORMONE TREATMENT







# APPENDIX

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- A. **Overview of Prader-Willi Syndrome**
- B. **Information Resources on Prader-Willi Syndrome**
- C. **Information Resources on Growth Hormone Use and Products**
- D. **Glossary of Terms**
- E. **Growth Hormone Studies of Children and Adults with PWS**
- F. **Historic June 2000 Announcement from PWSA (USA) of FDA Genotropin® Approval**
- G. **Growth Hormone Treatment and Prader-Willi Syndrome: PWSA (USA) Clinical Advisory Board Consensus Statement, June 2009**
- H. **Bibliography on PWS and Growth Hormone**
- I. **PWSA (USA) Growth Hormone Precautions Statement, February 2011**
- J. **Recommendations for Evaluation of Breathing Abnormalities Associated with Sleep in Prader-Willi Syndrome, December 2003**

# APPENDIX A.

## OVERVIEW OF PRADER-WILLI SYNDROME

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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. 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 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 underactivity, 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 adults;
- 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;
- 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

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### Prader-Willi Syndrome Association (USA)

PWSA (USA) is a national membership organization for families, professionals and service providers, and is a major source of information and research support on Prader-Willi syndrome in the United States. PWSA (USA) supports research and offers information, crisis assistance, publications and multimedia products; a bimonthly member newsletter, *The Gathered View*; and a national conference for families, service providers and scientists. PWSA (USA) also has a network of state and regional chapters, a Scientific Advisory Board, Clinical Advisory Board, Professional Providers Advisory Board, and an Adults with PWS Advisory Board. For a free information packet about the syndrome and membership in PWSA (USA), please use any of the following points of contact:

#### PWSA (USA)

8588 Potter Park Drive, Suite 500

Sarasota, FL 34238

Toll-free: 800-926-4797

Local: 941-312-0400

Fax: 941-312-0142

Website: <http://www.pwsausa.org>

The PWSA (USA) 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.

# INFORMATION RESOURCES ON GROWTH HORMONE USE AND PRODUCTS

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### **Human Growth Foundation**

997 Glen Cove Ave., #5  
Glen Head, New York 11545-1593  
Toll-free: 800-451-6434  
Local: 516-671-4041  
Fax: 516-671-4055  
E-mail: [hgfl@hgfound.org](mailto:hgfl@hgfound.org)  
Website: <http://www.hgfound.org>

The Human Growth Foundation (HGF) is a nonprofit membership organization of parents and professionals interested in growth disorders. HGF offers publications, a quarterly newsletter, an annual conference and e-mail discussion lists concerning growth issues in children and adults. HGF's website contains a number of informative articles about growth and deficiency treatment.

### **The MAGIC Foundation for Children's Growth**

(Major Aspects of Growth in Children)  
6645 W. North Ave.  
Oak Park, Illinois 60302  
Toll-free: 800-362-9423  
Local: 708-383-0808  
Fax: 708-383-0899  
Website: <http://www.magicfoundation.org>

The MAGIC Foundation is a nonprofit membership organization providing support and education regarding growth disorders in children and adults. It offers brochures, newsletters (print and online, for members only), national networking, including an e-mail discussion list for families of children with GH deficiency, and an annual convention. MAGIC's website has many free brochures on various aspects of growth and deficiency treatment.

### **American Association of Clinical Endocrinologists (AACE)**

AACE updated its "Medical Guidelines for Clinical Practice for Growth Hormone Use in Growth Hormone-Deficient Adults and Transition Patients" in 2009. These guidelines contain a great deal of information on the use of growth hormone and appear under AACE Guidelines on the AACE website: <http://www.aace.com>

### **Growth hormone manufacturers' websites**

Manufacturers of synthetic growth hormone have helpful websites with general information about GH, as well as specific information on their products.

(See listings on pages 44-47.)

## GROWTH HORMONE PRODUCTS

Following is information about the major synthetic growth hormone products available for sale in the United States in 2011 and the companies that produce them. These seven brands are identical to human growth hormone in molecular structure and are prescribed interchangeably. The products are nearly identical in composition, efficacy and cost, varying primarily in the formulations and delivery devices. There are a number of variations in product lines, especially in final formulations (diluent and preservatives used) and in the mixing and injection methods offered. GH injection devices and options continue to change. Manufacturers' websites should be checked for the latest information.

All of these manufacturers offer patient support programs, including insurance assistance and provision of medication for the uninsured and underinsured.

### *GH Product*

#### **Genotropin®**

### *Manufacturer*

**Pfizer**, New York, NY

<http://www.pfizer.com>

### *GH information website*

<http://www.genotropin.com/>

### *Special product features*

Double-chamber cartridge allows GH powder and liquid to be mixed without use of syringes

Genotropin Pen® — with a needle guard to hide needles from view, customizable Geno-Caps® and a user-friendly digital dose display; 5 or 12 mg multidose unit; allows click-dialing of a day's dosage

MiniQuick® — premeasured disposable syringes. An ideal travel choice, it's prefilled and portable. Requires no refrigeration for up to three months before reconstitution. Available in 10 dosage strengths. Preservative free.

Genotropin Mixer®, featuring a standard syringe system with flexible dosing.

### *Patient support program*

"The Pfizer Bridge Program" — 800-645-1280. Assistance with insurance.

*GH Product***Humatrope®** (Somatropin rDNA)*Manufacturer***Eli Lilly and Company**, Indianapolis, IN  
<http://www.lilly.com>*GH information website*<http://humatrope.com>*Special product features*

HumatroPen™ — multidose unit; allows click-dialing of day's dosage (user first injects liquid diluent into powder cartridge with a separate syringe unit). 6, 12 and 24 mg. pens

*Patient support program*

800-545-5979 or 800-847-6988

“Humatrope Reimbursement Center”

“Humatrope Access Program”

*GH Product***Norditropin®***Manufacturer***Novo Nordisk Pharmaceuticals, Inc.**, Princeton, NJ  
<http://www.novonordisk.com>*GH information website*[http://www.novonordisk.com/therapy\\_areas/growth\\_hormone/public/default.asp](http://www.novonordisk.com/therapy_areas/growth_hormone/public/default.asp)<http://www.norditropin-us.com/parents/nordiflex.asp><http://www.norditropin-us.com/flexpro/index.html>*Special product features*

FlexPro® — premixed, multidose GH pen can be used with FlexProPenMate®. Can be personalized with skins and charms. Smaller pen for child's smaller hand. 5, 10 or 15 mg.

FlexProPenMate® — an automatic needle insertion accessory with hidden needle

NordiFlex® — prefilled, multidose GH pen, can be used with NordiFlexPenMate®. Available in 30 mg.

NordiFlexPenMate — an automatic needle insertion accessory with hidden needle

*Patient support program*

888-NOVO-HGH (668-6444)

“NordiCare” — Reimbursement Hot Line assists with insurance coverage and claims submission.

“JumpStart” — Provides 28-day, no-charge supply of Norditropin cartridges to qualified patients working to access insurance benefits.

“Patient Access Program” funds medication for patients with limited/no insurance coverage.



*GH Product*

**Nutropin®**

*Manufacturer*

**Genentech, Inc.**, South San Francisco, CA

<http://www.genentech.com/>

*GH information website*

<http://www.nutropin.com/index.jsp>

*Special product features*

Nutropin AQ NuSpin® — Liquid GH from a prefilled, automatic device. Available in 5, 10 and 20 mg.

Nutropin AQ Pen® — Liquid GH from a cartridge, delivered by a device. Available in 10 and 20 mg.

Nutropin AQ® with vial and syringe — liquid GH for use with a syringe. Available in 10 mg.

Nutropin Vial and Syringe — GH in dry powdered form, to be mixed with a special fluid for use with a syringe. Available in 5 and 10 mg.

*Patient support programs*

866-NUTROPIN (688-7674)

“Nutropin GPS (Growing Patient Support) — assistance with insurance, free nurse hotline, injection training  
Genentech Access to Care Foundation — Help for uninsured patients

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*GH Product*

**Omnitrope®**

*Manufacturer*

**Sandoz, Inc.**, Princeton, NJ

609-627-8500

<http://www.sandoz.com/index.shtml>

*GH information website*

<http://www.omnitrope.com>

*Special product features*

Omnitrope® — liquid GH injection pen available in 5 and 10 mg.

Omnitrope® — 5.8 mg vial for reconstitution for use with syringe.

*Patient support program*

OmniSource — provides insurance assistance, injection training, and the

Sandoz Patient Assistance Program — assists in obtaining Omnitrope to uninsured and underinsured patients

877-456-6784

*GH Product*

**Saizen®**

*Manufacturer*

**Merck**, Rockland, MA

800-283-8088

<http://www.merck.de/en/index.html>

*GH information website*

<http://www.howkidsgrow.com>

*Special product features*

Easy Pod® — fully automated injection device for GH delivery

Cool.click™2 needle-free pen — injects GH through the skin with a blast of air

*Patient support program*

“Connections for Growth” — 800-582-7989

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*GH Product*

**Tev Tropin®**

*Manufacturer*

**Teva Pharmaceuticals, USA**, North Wales, PA

888-TEVA-USA (838-2872)

<http://www.tevabiologics.com/>

*GH information website*

<http://www.tev-tropin.com/>

*Special product features*

Tev-Tropin® — Reconstitute dry powder with diluent for use with a syringe

T-Jet® Device — needle-free device for use with Tev-Tropin®

*Patient support program*

“Growth Solutions” — injection training and education, as well as insurance and reimbursement assistance

866-TEV-TROP (838-8767)

## APPENDIX D.

# GLOSSARY OF TERMS

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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

### **Epiphysis**

The layer of cartilage at the ends of the skeletal bones where new cell growth occurs in children; when the epiphysis "closes," all cartilage has hardened into bone and no further growth is possible; also called the growth plate

### **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-I

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

### IGFBP-3

IGF binding protein-3; the substance that carries IGF-I 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

### M<sup>2</sup>

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

### 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

Breathing, lung function

### 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

### 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 calipers to determine the thickness of flesh 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 E.

# GROWTH HORMONE STUDIES OF CHILDREN AND ADULTS WITH PWS

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**EDITOR'S NOTE:** This summary of methods and findings is presented alphabetically by country. Please consult the bibliography in Appendix H for complete citations.

### GERMANY

#### **One-Year Results of Growth Hormone Treatment of Short Stature in Prader-Willi Syndrome (Hauffa, et al., *Acta Paediatrica Supplement*, November 1997)**

**Participants:**

17 prepubertal children, ages 3-12, with projected final height <3rd percentile for Germans

**Study Description:**

Eight children received GH treatment at a starting dose of 0.075 IU/kg/day for one month, followed by an increase to 0.15 IU/kg/day (up to a maximum dose of 8 IU/day) for the next 11 months. The remaining nine children received no GH treatment during the year. Measurements were taken for both groups at the start and at one year.

**Results:**

- Height velocity increased significantly (+5.5 SD) for the treated group and decreased for the controls
- GH treatments result in height increase (+1.07 SD) without acceleration of bone age advancement
- IGF-I and IGFBP-3 levels in the blood also increased significantly
- No differences found between the groups in weight and body composition (measured as skinfold thickness and waist:hip ratio)

### SWEDEN-DENMARK-NORWAY

#### **Two Years of Growth Hormone Therapy Improves Body Composition in Adults with Prader-Willi Syndrome (Rasmus Sode-Carlson, et al., Presented in May 2010 in Taipei, Taiwan at International Prader-Willi Syndrome Organisation 7th Scientific Conference)**

**Participants:**

46 adults with PWS (25 women and 21 men); median age, 29 years

**Study Description:**

This Scandinavian study was undertaken in an effort to confirm and substantiate the results of three previous studies that adults with genetically verified PWS experienced beneficial effects of growth hormone treatment upon body composition. Only one of the three earlier studies had the optimal randomized controlled design.

The patients in this project were randomized to treatment with GH or placebo for 12 months. During the following 12 months all patients were treated with GH according to their IGF-I value. Body composition was measured yearly by dual x-ray absorptiometry.

### Results:

In this first large-scale, long-term placebo-controlled study the improvement in body composition by GH treatment in adults with PWS was confirmed. No side effects were observed. Based on our two-year results, findings persist during long-term therapy.

## Growth Hormone Treatment of Children with Prader-Willi Syndrome Affects Linear Growth and Body Composition Favourably (Lindgren, et al., *Acta Paediatrica*, January 1998)

### Participants:

29 prepubertal children, ages 3-12 years

### Study Description:

Children were observed for six months, followed by random assignment to treatment (15 children) or control group (14). A non-PWS control group — 10 normal, obese children, ages 5-12 — was also studied. The GH treatment group received 0.1 IU/kg/day. Diet was controlled throughout the study to keep energy intake at same level per kg of body weight.

### Results at One Year:

- Increase in height velocity (+6.0 SD), from 4.1 cm/yr to 11 cm/yr
- 25% reduction in fat mass in treated group (measured by BIA, DEXA and CAT scan of thigh)
- 30% increase in fat-free mass in treated group
- Increase in fasting insulin levels and IGF-I levels in treated group
- No severe progression of scoliosis in either PWS group
- No difference found between the treated and untreated PWS groups in progression of bone age or puberty, in bone mineral density, or in calorie intake

### Study Continuation in Sweden:

Nine children from the treatment group in the first year of the study continued treatment at 0.1 IU/kg/day for a second year. Another nine children from the untreated PWS control group began GH treatment at a dose of 0.2 IU/kg/day. After one year, both groups stopped GH treatment for six months, then were restarted, all at the lower dose of 0.1 IU/kg/day. Treatment was continued through five years from the start of the original study.

### Results at Five Years:

- At both dosage levels (0.1 and 0.2 IU), BMI decreased significantly during the first year of treatment, then increased again during the six months without treatment, with a significant rise among those who had been treated only one year and at the higher dose of GH
- At both dosage levels (0.1 and 0.2 IU), height increased significantly during the first year of treatment
- Fasting insulin levels increased in both groups with GH treatment, and rose above normal levels in the higher dose group (two children developed Type 2 diabetes after rapid weight gain and stopped GH treatment in order to resolve it)
- After five years of GH treatment, participants maintained above-average growth rate for their age, and four children reached their final heights within  $\pm 2$  SD of their target heights

## SWITZERLAND

### **Treatment with Human Growth Hormone in Patients with Prader-Labhart-Willi Syndrome Reduces Body Fat and Increases Muscle Mass and Physical Performance (Eiholzer, et al., *European Journal of Pediatrics*, Vol. 157, 1998)**

#### **Participants:**

12 children, ages 0.6 - 14.6 years

#### **Study Description:**

All were treated with GH at a dose of 24 IU/m<sup>2</sup>/week for one year. Effects were compared for three groups of the participants: Group 1 — overweight and prepubertal (six children, ages 3.8 - 7.0 years), Group 2 — underweight and prepubertal (three children, ages 0.6 - 4.1), and Group 3 — pubertal (three children, ages 9.2 - 14.6). Body composition was measured by DEXA in the two older groups.

#### **Results:**

- In all groups, height velocity, hand and foot length, and arm span increased, but the changes were smaller in the oldest group
- Body fat decreased (percent fat dropped 14 points for Group 1 and 4 points for Group 3), but did not reach normal levels
- The youngest, underweight children gained weight for height because of the increased muscle mass, while the overweight groups had a decrease in BMI, weight for height and skinfold thickness
- Muscle mass increased in all groups, but less dramatically in the oldest group
- Physical performance improved in four children who were tested

## THE NETHERLANDS

### **Efficacy and Safety of Long-Term Continuous Growth Hormone Treatment in Children with Prader-Willi Syndrome (van Wijngaarden et al., *Journal of Clinical Endocrinology and Metabolism*, Vol. 94, 2009)**

#### **Participants:**

55 children with a mean age of 5.9 years

#### **Study Description:**

Investigate effects of long-term continuous GH treatment on body composition, growth, bone maturation, and safety parameters during four years of continuous GH treatment (1 mg/m<sup>2</sup> · d). Data were annually obtained on fat percentage (fat%) and lean body mass (LBM) by dual-energy x-ray absorptiometry, height, weight, head circumference, bone age, blood pressure, and fasting IGF-I, IGF binding protein-3, glucose, insulin, glycosylated hemoglobin, total cholesterol, high-density lipoprotein, and low-density lipoprotein. SD scores were calculated according to Dutch and PWS reference values (SDS and SDSPWS).

#### **Results:**

Four years of continuous GH treatment in children with PWS improves body composition by decreasing fat%SDS and stabilizing LBMSDS and head circumferenceSDS and normalizes heightSDS without adverse effects. Thus, long-term continuous GH treatment is an effective and safe therapy for children with PWS. Fat%SDS was significantly lower after 4 years of GH treatment ( $P < 0.0001$ ). LBMSDS significantly increased



during the first year ( $P = 0.02$ ) but returned to baseline values the second year and remained unchanged thereafter. Mean  $\pm$  SD height normalized from  $-2.27 \pm 1.2$  SDS to  $-0.24 \pm 1.2$  SDS ( $P < 0.0001$ ). Head circumference SDS increased from  $-0.79 \pm 1.0$  at start to  $0.07 \pm 1.1$  SDS after 4 yr.  $\text{BMISDS}_{\text{PWS}}$  significantly decreased. Mean  $\pm$  SD IGF-I and the IGF-I/IGF binding protein-3 ratio significantly increased to  $2.08 \pm 1.1$  and  $2.32 \pm 0.9$  SDS, respectively. GH treatment had no adverse effects on bone maturation, blood pressure, glucose homeostasis and serum lipids.

### **Randomized Controlled Trial to Investigate the Effects of Growth Hormone Treatment on Scoliosis in Children with Prader-Willi Syndrome (van Wijngaarden et al., *Journal of Clinical Endocrinology and Metabolism*, Vol. 94, 2009)**

#### **Participants:**

91 children with PWS with median age of 4.7 years

#### **Study Description:**

The aim was to study the effects of GH treatment on the onset of scoliosis and curve progression. The prevalence of scoliosis in children with Prader-Willi syndrome (PWS) is 30–80 percent, depending on age. Although reports about effects of GH treatment on scoliosis in children with PWS are limited, scoliosis is generally considered a contraindication for GH treatment. We conducted a multicenter, randomized, controlled GH study in infants and prepubertal and pubertal children. Infants and prepubertal children were randomized into a GH-treated group ( $1.0 \text{ mg/m}^2 \cdot \text{d}$ ) and a control group for 1 and 2 yr, respectively. Pubertal children were randomized to receive somatotropin  $1.0$  or  $1.5 \text{ mg/m}^2 \cdot \text{d}$ . Yearly, x-rays of the spine were taken, and height, weight, truncal lean body mass (with dual energy x-ray absorptiometry), and IGF-I were measured.

#### **Results:**

GH-treated children had similar onset of scoliosis and curve progression as randomized controls ( $P = 0.27$ – $0.79$  and  $P = 0.18$ – $0.98$ , respectively). GH treatment, IGF-I SD score (SDS), and catch-up growth had no adverse effect on the onset of scoliosis or curve progression, even after adjustment for confounders. Height SDS, truncal lean body mass, and IGF-I SDS were significantly higher in GH-treated children than in randomized controls. At baseline, a higher IGF-I SDS was associated with a lower severity of scoliosis. Scoliosis should no longer be considered a contraindication for GH treatment in children with PWS.

### **Mental and Motor Development Before and During Growth Hormone Treatment in Infants and Toddlers with Prader-Willi Syndrome (Festen, et al., *Clinical Endocrinology*, Vol. 68, 2008)**

#### **Participants:**

43 infants with PWS

#### **Study Description:**

In an effort to evaluate psychomotor development in infants with Prader-Willi syndrome who are receiving growth hormone treatments, 29 of the 43 participants were randomized into a GH group ( $n=15$ ) receiving  $1 \text{ mg/m}^2/\text{day}$  GH or a non-GH treated control group ( $n=14$ ). At baseline and after 12 months of follow-up, analysis with Bayley Scales of Infant Development II (BSID-II) was performed. Data were converted to percentage of expected development age (%ed), and changes during follow-up were calculated.

**Results:**

Both mental and motor development improved significantly during the first year of the study in the GH group vs. the control group: median interquartile range change was +9.3% (-5.3 to 13.3) vs. -2.9% (-8.1 to 4.9) (P<0.05) in mental development and +11.2 % (-4.9 to 22.5) vs. -18.5% (-27.9 to 1.8) (P<0.05) in motor development, respectively.

## UNITED KINGDOM

### **Effect of Growth Hormone on Height, Weight and Body Composition in Prader-Willi Syndrome (Davies, et al., *Archives of Disease in Childhood*, Vol. 78, 1998)**

**Participants:**

25 children, ages 4-10

**Study Description:**

Children were observed for six months, followed by six months of GH treatment at a dose of 20 IU/m<sup>2</sup>/week in daily injections. Testing was done at start, six months and 12 months for height, weight, skinfold thickness and body composition (through measurement of total body water, using stable isotopes).

**Results:**

- Height velocity doubled, increasing height by an average 5.7 cm
- Percent body fat rose before GH treatment, and declined with treatment (from an average 36.7% at 0 months to 40.6% at six months and to 32.5% at 12 months)
- Skinfold thickness decreased
- Percent fat-free mass increased from 59.4% to 67.5%

## UNITED STATES

### **Growth Hormone Treatment of Adults with Prader-Willi Syndrome and Growth Hormone Deficiency Improves Lean Body Mass, Fractional Body Fat, and Serum Triiodothyronine without Glucose Impairment: Results from the U.S. Multi-Center Trial (Mogul, et al., *Journal of Clinical Endocrinology and Metabolism*, January 2008)**

**Participants:**

38 adults with PWS (25 women and 13 men); mean age of 30.5 years

**Study Description:**

Growth hormone (GH) replacement in children with PWS has well-defined benefits and risks and is used extensively worldwide. The objective of this project was to evaluate the effectiveness and safety of GH in GH-deficient genotype positive PWS adults at four academic medical centers over a 12-month period with six-month dose-optimization and six-month stable treatment periods. Human recombinant GH was initiated at 0.2mg/day with monthly 0.2mg increments to maximum 1.0mg/day, as tolerated.

**Results:**

LBM increased from 42.65([se]2.25) to 45.47[2.31]kg ( $P \leq .0001$ ) and %fat decreased from 42.84[1.12] to 39.95[1.34] % ( $P = .025$ ) at a median final dose of 0.6mg/day in 30 study subjects who completed 6-12 months of GH. Mean fasting glucose, 85.3[3.4]mg/dl, HbA1C 5.5[.2]%, fasting insulin 5.3[.6] $\mu$ U/ml, AUC-insulin 60.4[7.5]  $\mu$ U/ml. HOMA-IR[.2] were normal at baseline in 38 study initiators, including 5 diabetics, and remained in normal range. Total T3 increased 26.75%: 127.0[7.8] to 150.5[7.8]ng/dl ( $P = .021$ ) with normalization in all subjects, including 6(20%) with baseline T3's  $\geq 2$ SD's below mean. Mildly progressive ankle edema was the most serious treatment emergent adverse event (5 patients). This study demonstrates that GH improves body composition, normalizes T3, and is well tolerated without glucose impairment in PWS genotype adults.

### Final Adult Height in Children with Prader-Willi Syndrome with and without Human Growth Hormone Treatment (Angulo, et al., *American Journal of Medical Genetics, Part A*, 143A, 2007)

**Participants:**

21 individuals (8 females and 13 males), ages 15-20, who received growth hormone treatments and attained final adult height after 7.9 + 1.7 years; and 39 individuals (26 females and 13 males), ages 18-25, identified through the same database and who reached adult height without receiving growth hormone treatment.

**Study Description:**

The objective of this study was to compare adult heights attained in separate groups of males and females with Prader-Willi syndrome. One group of subjects had received growth hormone treatments; the second group had not received growth hormone treatments. Subjects were included in the study if they had reached adult height, determined as the height attained when the bone age reached 16 years for males and 14 years for females, and when growth velocity had reached a plateau ( $< 2$ cm/year).

**Results:**

Data revealed that the administration of growth hormone to children with Prader-Willi syndrome restores linear growth and final adult height without significant adverse events. In contrast, children with PWS who had not received growth hormone treatments had a significant decrease in growth velocity, with a mean final adult height under 2 standard deviations below the relevant population mean, and a higher risk for type 2 diabetes mellitus.

### Long-Term Growth Hormone Therapy Changes the Natural History of Body Composition and Motor Function in Children with Prader-Willi Syndrome (Carrel, et al., *Journal of Clinical Endocrinology and Metabolism*, Vol. 95, 2010)

**Participants:**

48 children (21, ages 6-9; and 27, ages 5-9)

**Study Description:**

To assess the impact of hGH therapy begun early in life on the natural history of PWS, we compared height, body composition and strength in similar-age children with PWS naïve to hGH with those treated with hGH for 6 years. Twenty-one subjects (aged 6-9 yr) treated with hGH for 6 years (beginning at 4-32 months, mean 13  $\pm$  6 months) were compared with 27 children of similar age (5-9 yr) prior to treatment with hGH. Percent body fat, lean body mass, carbohydrate/lipid metabolism, and motor strength were compared using analysis of covariance.

**Results:**

PWS children treated with hGH demonstrated lower body fat (mean,  $36.1 \pm 2.1$  vs.  $44.6 \pm 1.8\%$ ,  $P < 0.01$ ), greater height ( $131 \pm 2$  vs.  $114 \pm 2$  cm;  $P < 0.001$ ), greater motor strength [increased standing broad jump  $22.9 \pm 2.1$  vs.  $14.6 \pm 1.9$  in. ( $P < 0.001$ ) and sit-ups  $12.4 \pm 0.9$  vs.  $7.1 \pm 0.7$  in 30 sec ( $P < 0.001$ )], increased high-density lipoprotein cholesterol ( $58.9 \pm 2.6$  vs.  $44.9 \pm 2.3$  mg/dl,  $P < 0.001$ ), decreased low-density lipoprotein ( $100 \pm 8$  vs.  $131 \pm 7$  mg/dl,  $P < 0.01$ ), and no difference in fasting glucose or insulin.

**Conclusions:**

hGH treatment in children with PWS, begun prior to 2 years of age, improves body composition, motor function, height and lipid profiles. The magnitude of these effects suggests that long-term hGH therapy favorably alters the natural history of PWS to an extent that exceeds risks and justifies consideration for initiation during infancy.

**Growth Hormone Improves Body Composition, Fat Utilization, Physical Strength and Agility, and Growth in Prader-Willi Syndrome: A Controlled Study (Carrel, et al., *Journal of Pediatrics*, 134 (2), 1999)**

**Participants:**

54 children, ages 4-16

**Study Description:**

All were observed for six months; then 35 children were treated with GH at a dose of 1 mg/m<sup>2</sup>/day, and 19 were untreated controls for one year. In the second year, the control group also received GH treatment, all at the same initial dose. Comprehensive testing was done on all subjects, including behavioral surveys, diet records and bone x-rays, in addition to blood tests and measurements of height, weight, body composition, resting energy expenditure and physical performance.

**Results:**

- Treated children increased height, growth velocity and muscle mass during the two years, although growth rate slowed in the second year
- Head, hand and foot measurements approached normal averages during treatment, and the lower facial height exceeded average
- Treated children improved in running speed, sit-ups, broad jump and weight-lifting tests, compared with the control group
- Improvements in pulmonary function and physical performance during the first year were maintained during the second year, with further increases in arm strength and running speed
- Body fat decreased by an average 8 percentage points after one year of treatment, but did not decrease further during the second year
- 70% had mild scoliosis at the start of the study, and progression of the curves was similar in the treated and untreated groups
- Total cholesterol and LDL decreased, and HDL increased after one year of growth hormone treatment
- Resting energy expenditure started below average and increased in both groups, but more so in the treated children
- Bone mineral density started within normal ranges and increased at a greater rate in the treated children than in the controls
- GH treatment caused no deterioration in behavior and appeared to reduce depression, obsessive/compulsive symptoms and skin-picking

## Growth Hormone and Mortality in Prader-Willi Syndrome (Abstract By Phillip D. K. Lee, MD, FAAP, FACE [www.GGHjournal.com](http://www.GGHjournal.com) June 2006)

The administration of growth hormone (GH) has numerous benefits for individuals with PWS including a decline in the fat percentage of lean body mass, and improvement in body composition, agility and muscle strength. In the almost 20 years since the introduction of the use of GH in PWS, very few bad effects have been reported. However, two children with PWS who were receiving GH died in 2002. This led to a discussion about the safety of GH in PWS and ultimately resulted in the drug company, Pfizer, applying a warning label to its GH prescriptions. This warning stated that GH should not be used in those with PWS who are severely obese or have severe breathing problems. In 2004, other drug companies added the same warning to their GH drugs. This led to a tremendous amount of concern in the PWS community, as denying GH to individuals with PWS can be very damaging to their health and lifestyles.

Unfortunately, premature death in PWS has been a problem since long before GH was used as a treatment. Deaths are often due to cardio-respiratory illness, and none of the reported 190 deaths reported to PWSA (USA) since 1977 appear to be related to GH. Since May of 2006, 18 children and two adults worldwide with PWS died while receiving GH. Some of these deaths were due to causes completely unrelated to GH, such as drowning in a bathtub. Many of the deaths were in individuals who were significantly overweight, and almost all of the cases were not receiving the dose on the medication's label.

Some have suggested that GH can cause death in individuals with PWS with breathing problems. For individuals who appear to have died because of severe breathing problems, it is noted that these problems were present before GH treatment even began. In five out of six cases examined, cases of those with breathing problems, GH treatment did not make these types of conditions worse. Special analysis of sleep problems need not be standard for every individual being treated with GH. However, if an individual has a history of excessive daytime sleepiness or extreme breathing problems during sleep, a sleep analysis is recommended before GH treatment.

The concerns about GH and death in PWS are ultimately invalid for the following reasons: 1) deaths in infants with PWS are usually due to feeding aspiration, have nothing to do with GH treatment and should be closely monitored; 2) deaths in older children and adults with PWS are very often associated with obesity, and the insulin resistance associated with obesity may be increased by GH; this deserves special attention; 3) tub-drowning deaths have nothing to do with GH and should be addressed separately; 4) most of the deaths during GH treatment occurred with doses below the recommended amounts; doses should not be limited and should be well-monitored; 5) clinical follow-up is crucial to preventing deaths which are attributed to GH treatment, as almost all of the reported deaths occurred within the first 18 months of treatment; and 6) sleep analysis should not be required for GH treatment unless the patient has an outstanding history of breathing problems which merit further examination before treatment begins. *(This opinion is not held by most PWS experts who believe a sleep study should be done. See Appendix G, Growth Hormone Treatment and Prader-Willi Syndrome: PWSA (USA) Clinical Advisory Board Consensus Statement, June 2009.)*

GH as a treatment for those with PWS has led to improvements in height and appearance in addition to providing "a new outlook on life." Further population studies and more thorough follow-up with patients will add to our knowledge of GH and will lead to a better understanding of how to best administer GH while sparing the seemingly unnecessary association between deaths in PWS and this life-altering treatment.



Prader-Willi  
Syndrome  
Association  
U.S.A.

\*

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## APPENDIX F. 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](http://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](http://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  
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 G.**

# **GROWTH HORMONE TREATMENT AND PRADER-WILLI SYNDROME: PWSA (USA) CLINICAL ADVISORY BOARD CONSENSUS STATEMENT, JUNE 2009**

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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<sup>1-4</sup>. 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<sup>1-5</sup>. 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<sup>6-8</sup>.

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<sup>9</sup>. 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<sup>3,10</sup>. 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 before and ~ 6-12 weeks after beginning GH treatment<sup>10</sup> 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<sup>11,12</sup>. 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 H.

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# APPENDIX I.

## PWSA (USA) GROWTH HORMONE PRECAUTIONS STATEMENT, FEBRUARY 2011

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We advocate a sleep study before the start of growth hormone (GH) on infants, children and adults with Prader-Willi syndrome (PWS), and then a follow-up study 6-8 weeks later. If there is worsening of obstructive sleep apnea (OSA) while on GH, temporarily stopping the GH is recommended until the cause is understood. Frequently, the OSA can be corrected by removing the adenoids and tonsils or lowering the dose of GH (in the face of an abnormally high IGF-1). We also recommend taking precautions during bouts of upper respiratory infections.

There are reports and discussions in the medical literature about adrenal hypofunction in PWS. Single measures of cortisol levels will not be helpful and adrenal challenge tests may be warranted. Please consult an endocrinologist for input and advice before starting growth hormone treatment.

Infants with PWS may have gastroesophageal reflux disease (GERD), which causes obstructive hypopneas/apneas. If an evaluation is positive for GERD, an anti-reflux medication may be prudent before starting GH.

Studies have shown that in most individuals with sleep-disordered breathing due to PWS, GH can actually improve (or at least does not worsen) the apnea (Haqq, et al., 2004; Miller, et al., 2006; Festen, et al., 2006). Withholding GH from those with sleep apnea may be detrimental on several levels. Therefore, the recommended approach is that children with PWS be monitored closely when starting GH to make sure they do not worsen.

The FDA has a statement warning that there could be an increased risk of death associated with GH due to a recent study in France indicating that there may be a slightly increased risk of death in certain individuals treated with GH. PWS is not one of the groups mentioned as being at increased risk; they specifically mention idiopathic short stature and isolated GH deficiency.

Jennifer Miller, M.D., M.S. – Endocrinologist, PWSA (USA) Clinical Advisory Board member  
Merlin G. Butler, M.D., Ph.D. — PWSA (USA) Scientific Advisory Board Chairperson  
Daniel J. Driscoll, M.D., Ph.D. — PWSA (USA) Clinical Advisory Board Chairperson

## APPENDIX J.

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

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*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.

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** (see “Medical News” article regarding “Anesthesia and PWS” written by Drs. Loker and Rosenfeld in *The Gathered View*, vol. 26, Nov. — Dec., 2001 or visit [www.pwsausa.org](http://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.

Members of the Clinical Advisory Board are available for consultation with physicians and families through the Prader-Willi Syndrome Association (USA).

Prader-Willi Syndrome Association (USA)  
8588 Potter Park Drive, Suite 500  
Sarasota, Florida 34238

Telephone: 800-926-4797 or 941-312-0400



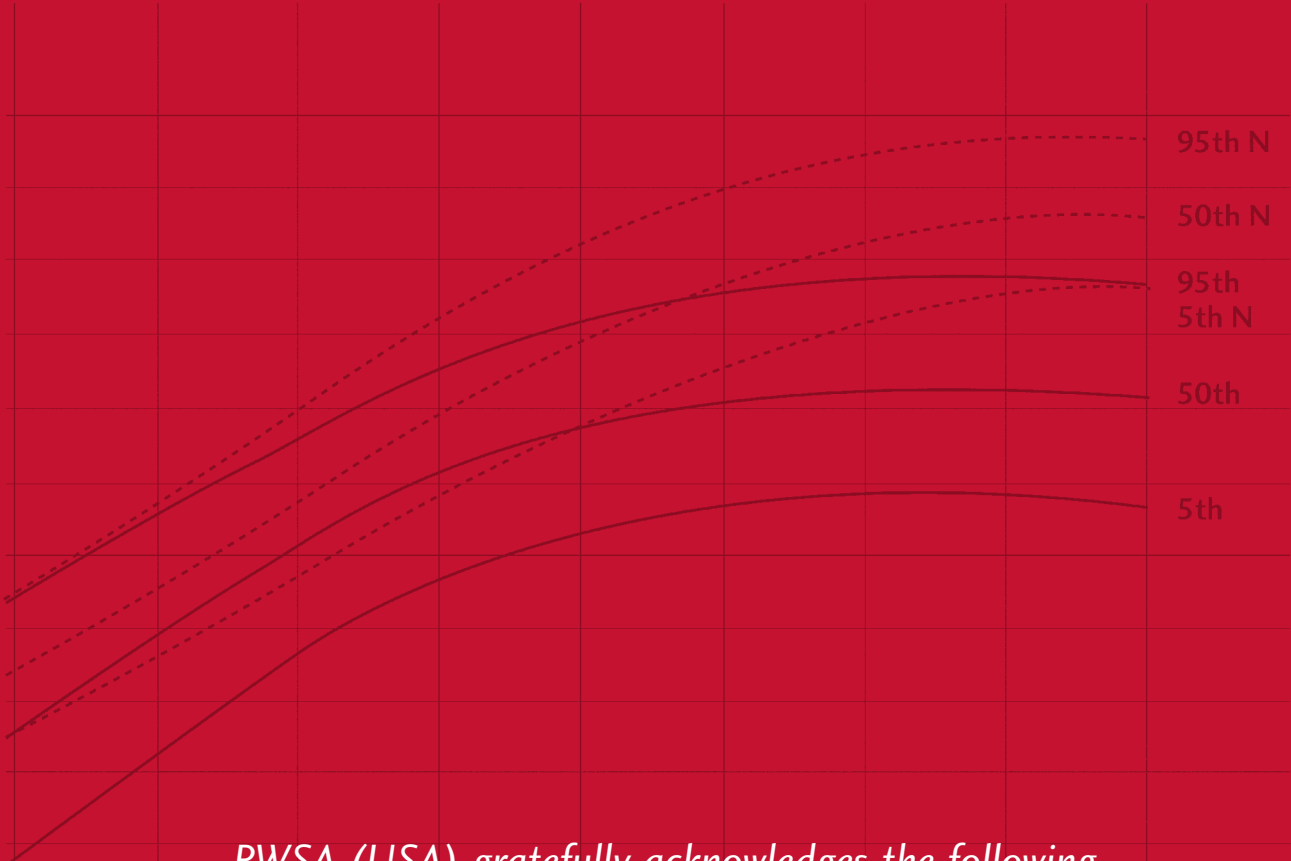


## MILESTONES

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- 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)





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*Together We Are Saving Lives*