

**Exhibit: A**

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Date April 18, 2013

The current approval for using Growth Hormone (Genotropin) for individuals with Prader-Willi Syndrome is found IDAPA 16.03.09.663.01b - which states "Pharmaceutical items requiring prior authorization include: Growth hormones".

Apparently that ' authorization ' is based on the following approval standards: (*Exhibit B*)

Prader-Willi Syndrome (ICD-9 759.81)

o Medical necessity documentation for growth

o Baseline and annual monitoring for obstructive sleep apnea and scoliosis

*This rationale for approval does not appear to be reflective of current medical standards of care for this condition* and it is our contention that this basis for approval is not based on accepted use of Growth Hormone for PWS, or FDA approval standards for the use of Growth Hormone.

**Standards of GH use for PWS individuals:**

**1. GH for PWS not just about height/growth:**

- a. "GH plays an important role in longitudinal bone growth and maturation during childhood and adolescence. **However, GH has important metabolic functions other than bone growth, which becomes more apparent during young adulthood, when growth has been completed.**" *Saggese G, Baroncelli GI, Vanacore T, Flore L, Ruggieri S, Federico G. Department of Reproductive Medicine and Pediatrics, University of Pisa, Pisa Italy. Indications and Strategies for continuing GH treatment during transition from late adolescence to early adulthood in patients with GH deficiency: the Impact on bone mass. J Endocrinol Invest. 2004 Jun; 27 (6): 596-602.*

Dr. Boston, her endocrinologist stated to us that Growth Hormone should not be even called Growth Hormone due to the many other important roles it plays. Indeed, GH deficiency (GHD) in adult life is a recognized clinical syndrome which includes symptoms such as increased central adiposity, decreased lean body mass, reduced bone mineral density (BMD), increased atherogenic risk, cerebrovascular and cardiac morbidity and mortality, and reduced quality of life. As approximately one quarter of the children with GHD should continue GH administration in adulthood, it is important to reconfirm GHD at the end of growth in order to select patients with Severe GHD who need to resume GH therapy with an appropriate age-related dosage. Some evidence indicates that most peak bone mass (PBM) is achieved by the end of adolescence but small increased in BMD continue during the period of transition from late adolescence to young adulthood

- b. "GH deficient (GHD) adult patients, either from child-or adulthood onset, have impaired health (impairment in body composition and structure functions as well as derangement in lipoprotein and in carbohydrate metabolism leading to increased cardiovascular morbidity\_, which improves with GH replacement. **For patients with childhood-onset GHD, the so called "transition phase", defined as the period between reaching the final height and the completion of the development of such organs, can be considered as the most important phase of life for the development of important**

**target organs: heart, bones and muscles.** Particularly, children with GHD may not attain the peak bone mass (PBM) at the time of discontinuation of GH therapy, as the complete achievement of PBM is likely reached later on, during the transition phase to adulthood. In addition, patients with GHD generally have a delayed timing of PBM compared to normal individuals. GH treatment should be continued until the attainment of PBM, independently of the final height achieved. Individual titration of the recombinant human GH (rhGH) dose is recommended, and measurement of IGF-I levels is needed for monitoring the adequacy of replacement. The GH dose for replacement in the transition adolescent is still higher than in adulthood; after puberty, the rhGH dose should be progressively decreased in the following years (probably up to at least 25 yr of age) in order to obtain the achievement of optimal PBM". *Aimaretti G, Corneli G, Rovere S, Crace CG, Ghigo E, Procopio M. Division of Endocrinology and Metabolism, Department of Internal Medicine, University of Turin, Turin, Italy. Is GH therapy useful to preserve bone mass in transition-phase patients with GH deficiency? J Endocrinol Invest. 2005; 28 (10 suppl): 28-32.*

- c. Genotropin is a biosynthetic, recombinant human GH that has an identical amino acid sequence to naturally occurring GH made in the pituitary gland. As such, it stimulates linear skeletal growth in patients with PWS. **Additional effects of Genotropin include increased protein synthesis, increased muscle mass, reduced fat mass, beneficial effects on lipid metabolism, and alterations in carbohydrate metabolism.** *Genotropin® Prescribing Information. Pfizer. 2004.*
- d. See also Exhibits: C, D, E, F, G, H, I, J, K

2. **PWS Individuals have Deficient GH levels:**

a. "In the general population, growth hormone deficiency causes not only short stature, but also hypotonia, decreased muscle mass and increased fat mass (i.e., altered body composition), central obesity, osteopenia, small hands and feet, delayed bone age, and low IGF-1. All of these are present in PWS. Reports based on recent double-blind crossover studies of rhGH treatment in PWS have indicated dramatic increase in growth rate (especially in the first year of treatment) and a variety of other effects, including: 1) improved body composition (higher muscle mass, lower fat mass), 2) improved weight management; 3) increased energy and physical activity; 4) improved strength, agility and endurance; and 5) increased respiratory muscle forces". *Suzanne B. Cassidy<sup>1</sup>, Ellen Simpson<sup>1</sup>, Shauna Heeger<sup>2</sup> - <sup>1</sup>Division of Human Genetics, Department of Pediatrics, University of California, Irvine, 101 The City Drive, Bldg 2, Orange, CA 92868, (714) 456-6261, and <sup>2</sup>Case Western Reserve University. - (Exhibit K)*

b. "In conclusion this pilot study showed that adults with PWS have a partial GH deficiency, and GH treatment has beneficial effects on body composition in adult PWS without significant side-effects". *Höybye C. - Department of Endocrinology and Diabetology, Karolinska Hospital, Stockholm SE-171 76, Sweden. charlotte.hoybye@ks.se Growth Horm IGF Res. 2004 Feb;14(1):1-15 - (Exhibit F)*

3. **GH therapy can have great benefits for PWS adults**

a. "Recent studies indicate that adults with PWS continue to have the same GH deficiency that was present in childhood, with the same health risks attendant to non-PWS, GH-deficient adults. Most adults with PWS also are deficient in sex-steroid/sex hormone production, which further increases the health risks associated with GH deficiency. Thus, in addition to a possible improved body composition, the potential for

improved long-term health strongly suggested the need to study GH therapy for adults with PWS.

J **Significant improvement in body composition is observed in adults with PWS**, both males and females, treated with GH replacement therapy. These include increased muscle mass, and for many, a reduction in fat tissue. There also appears to be a small positive impact on bone mineral density;..." - *Barbara Y. Whitman, Ph.D, Growth Hormone for Adults with Prader-Willi Syndrome - (Exhibit E)*

X b. "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 years results, findings persist during long-term therapy" - *Two year of growth hormone therapy improves body composition in adults with Prader-Willi Syndrome: May 2010, Rasmus Sode-Carlson1, Jens Bollerslev2, Thomas Schreiner2, Jens Sandahl Christiansen3, Stense Farholt1, Kai Fr. Rabben4, Charlotte Høybye5 - (Exhibit J)*

#### X 4. **Growth Hormone was approved by FDA for Prader-Willi Syndrome**

- a. Genotropin recombinant GH was approved by the FDA in 2000 and granted orphan drug status as a safe and effective long-term treatment for growth failure in children with PWS.

#### **Growth Hormone therapy for PWS individuals would not be over burdensome for Idaho**

The current census of individuals with PWS residing in Idaho is 27. To provide GH therapy for these few individuals would not over-burden Idaho's budget, and yet this therapy can make a significant change in each individual's quality of life, the lives of their care givers and help them to be a contributing part of society instead of a drain.

Please be aware that our daughter is a continuing therapy patient. Growth hormone therapy is not only used to promote linear growth, but for PWS is essential to increase bone density, lean tissue, decrease adipose tissue, bolster cardiac contractility, improving mood and motivation, enhance exercise capacity, and modulate the metabolism of lipoprotein. Without GH therapy, Katherine's quality of life will be greatly diminished. We might also add, as a care giver; caring for a PWS individual is extremely difficult. It is stressful, we must be on constant guard to prevent over-eating, locking all food sources, dealing with tantrums, acting out, moodiness, and dealing with innumerable health issues. In our experience, we have seen that GH therapy reduces all of these issues.

#### **History:**

Katherine was diagnosed at birth with Prader-Willi Syndrome. Although Growth Hormone was approved for children with this syndrome, she did not receive it until the age of eight because of Idaho's slow and reluctant approval process. She lost those eight years of the benefit of Growth Hormone that could have made a difference in her life. While we have been informed by other PWS families and professionals that you will most likely turn this request down based on legal word twisting, the fact of an individual's need for a drug (in her case what is termed "Growth Hormone") is a reality. Consider if the child were your own and his/her potential to be a functioning member of society in spite of their disability was hinged on receiving this drug; and without it only a future of downhill dependency, most likely becoming obese and non productive.

We witnessed the difference when she was eight before receiving Growth Hormone. At that time, she could not hold her head or body straight. Her eyes wandered excessively. (*See Exhibit: L*)

Her need for physical therapy and other therapies reduced as she blossomed before our eyes with the

addition of Growth Hormone, including her mental focus. Height was a minor consideration as our family is short anyway, and Katherine is only 4' 11" at her full adult height. we hate to see her change again from an almost normal seeming state to one of obvious disability. This drug is vital to persons with Prader-Willi Syndrome.

While we fully understand the need to manage growing costs of healthcare through the development and implementation of policy, we nonetheless feel that it is important that such policy leave room for individual consideration. To do so otherwise is a disservice to our daughter and perhaps the other 27 or so individuals with Prader-Willi syndrome who live in Idaho. Yes, just 27 to whom a life changing difference can be made.

Considering Katherine is a continuing therapy patient whose GH treatment has been covered by this Idaho Medicaid for years, her risk for hyperlipidemia, early heart disease, and other health risks; it is apparent that Katherine should continue with her course of growth hormone therapy. We therefore request that the case be reconsidered for recertification of growth hormone therapy.

Continued treatment of adults with PWS who were previously treated for growth failure as children is an acceptable standard of medical care to prevent the loss of muscle development, fat reduction, and increased energy levels maintained while receiving therapy throughout childhood.<sup>9</sup> ***Proof of growth hormone deficiency by stimulation testing in individuals born with PWS is not required by the FDA or by current clinical practice standards.*** Failure to continue growth hormone is known to contribute significantly to complications from obesity in PWS including sleep apnea, type II diabetes, muscle weakness, lethargy, premature atherosclerosis, metabolic diseases, and cor pulmonale.<sup>9,14</sup>

***We are requesting review of this authorization policy based on currently accepted standards of medical care. We request that Idaho Medicaid be required to allow GH therapy for all individuals with Prader-Willi syndrome in Idaho.***

In order to assist you with this review, we have included the physician's notes summarized in Exhibit B with additional Exhibits supporting the critical need for GH treatment in adults with PWS.

Sincerely,  
Bruce and Margaret Jenkins  
Parents of Katherine Jenkins (PWS)

**Idaho Medicaid – Therapeutic Criteria for Growth Hormone**  
**Approved by Pharmacy & Therapeutics Committee**  
Last Updated: May 2011

**Diagnoses and Criteria**

**Chronic Renal Impairment (ICD-9 585)**

- Patient is awaiting renal transplant
- PTH level no greater than 2x target upper limit for CKD Stages 2-4 or 1.5x target upper limit for CKD Stage 5
- Phosphorus no greater than 1.5x upper limit for age
- No active rickets
- Slipped capital femoral epiphysis (if present) is resolved
- Medical necessity documentation for growth

**Growth Hormone Deficiency (ICD-9 253.2, 253.3)**

- Growth hormone stimulation testing
- Hypothyroidism treatment, if clinically appropriate, has been started
- Medical necessity documentation for growth

**Prader-Willi Syndrome (ICD-9 759.81)**

- Medical necessity documentation for growth
- Baseline and annual monitoring for obstructive sleep apnea and scoliosis

**Turner Syndrome (ICD-9 758.6)**

- Medical necessity documentation for growth

**Idiopathic Short Stature (ICD-9 783.43)**

- Payment for growth hormone for this diagnosis is not authorized by Idaho Medicaid under IDAPA 16.03.09.04.h which states that “drugs for cosmetic use are excluded from coverage”

**Small for Gestational Age (ICD-9 764)**

- Payment for growth hormone for this diagnosis is not authorized by Idaho Medicaid under IDAPA 16.03.09.04.h which states that “drugs for cosmetic use are excluded from coverage”

**HIV Cachexia (ICD-9 042, 079.53)**

- Only approved for adults for this diagnosis
- Initial approval for 12 weeks, extension of therapy on a case-by-case evaluation
- Not covered for HIV-associated adipose redistribution syndrome (cosmetic indication excluded from coverage under IDAPA 16.03.09.04h)

**Acceptable Growth Hormone Stimulation Testing**

Growth hormone stimulation panel with arginine or levodopa with peak growth hormone levels < 10 mcg/ml

OR

Insulin tolerance test with peak growth hormone levels < 10 mcg/ml

OR

An equivalent diagnostic test

**Medical Necessity Documentation for Growth**

**For initial approval only**

Height 2 or more standard deviations below mean or less than 3<sup>rd</sup> percentile of normal for age and sex

**For initial approvals AND annual renewals (all of the following must be met)**

Increase in height of at least 2 cm over the past year

AND

Bone age: female < 14 years and male < 16 years. The radiology report should include standard deviation and/or confidence intervals

AND

Documentation of open epiphyses within the previous six months

AND

No expanding lesion or tumor diagnosis

AND

Chronological age < 18 years.

**Documentation Required for Prior Authorization Requests**

Physician notes documenting the diagnosis AND

Endocrinologist is initiating the growth hormone therapy AND

Most recent endocrinologist's office visit note AND

Current growth chart AND

Most recent bone age AND

Results of growth hormone stimulation testing, if required for diagnosis (for initial approval)

## Exhibit: C

### Patient Condition

Katherine is currently a 16 year old young WOMAN who was diagnosed with PWS shortly after birth by genetic testing.

In August 2005, at the age of 8, Katherine was subsequently referred for endocrine evaluation and treated with GH for growth failure associated with PWS per FDA prescriptive guidelines. **Dr. Bruce Boston of OHSU is now recommending continuation of GH therapy for Katherine in view of findings in the current peer reviewed medical literature demonstrating that treatment with GH in adults with PWS:**

- *normalizes body proportions*<sup>7</sup>,
- *improves body composition*<sup>8</sup>,
- *normalizes IGF-1*<sup>10</sup>,
- *normalizes lipid profiles*<sup>10</sup>,

On January 28, 2013, Katherine's most recent visit, her height was 148 cm and her weight was 51.4 kg. A skeletal x-ray, obtained 11/17/2013, revealed a bone age of 14 years at chronological age 16 years 3 months indicating Katherine still has time to grow.

As described in more detail below, PWS is characterized by hypothalamic dysfunction, ultimately resulting in obesity, osteoporosis, and marked reduction in muscle mass. Intervention with GH increases body muscle mass, affects physical strength and agility, respiratory function, and bone mineral density. The results of Katherine's recent DEXA scan demonstrate that GH has had a positive impact on her bone mineral density and IGF-1 stability.

### Description of PWS

PWS is a very rare genetic disorder for which there is no cure. However, several treatments in place to lessen the condition's symptoms. Short stature is one of these symptoms; however, the uncontrollable hunger that produces the largest problem associated with PWS; severe obesity. Hyperphagia and obesity usually begin between ages one and six years. Hyperphagia is believed to be caused by a hypothalamic abnormality resulting in lack of satiety. Food-seeking behavior, with hoarding or foraging for food, eating of inedibles, and stealing of food or money to buy food, are common. Gastric emptying is delayed. Obesity results from these behaviors a decreased total caloric requirement, resulting from decreased resting energy expenditure resulting from decreased activity and decreased lean body mass.

Prader-Willi syndrome is a genetic disorder characterized by short stature, hypogonadism, small hands and feet, low muscle tone, and cognitive disabilities.<sup>1</sup> The syndrome occurs in 1 out of every 10,000 to 15,000 births.<sup>1</sup> Patients with PWS have high rates of morbidity in addition to short stature. The disorder is the most common genetic cause of obesity, and is associated with delayed or absent puberty.<sup>1</sup>

## Treatment of PWS

X All available medical evidence indicates that growth hormone therapy (GHT) is an essential standard treatment for individuals with PWS. Individuals with PWS have hypothalamic dysfunction and, thus, multiple hormone deficiencies. Replacement of growth hormone in the Prader- Willi population has been shown to have significant positive effects, including decreased fat mass, increased muscle mass, increased strength and tone, improvement in lipid profile, improvement in central sleep apnea, improved responsiveness to increased levels of carbon dioxide and increased bone mineral density. And, it may also allow them to eat more calories and not experience extraordinary weight gain. Without growth hormone therapy, individuals with PWS struggle to maintain their weight on 800-1000 calories per day. Many develop obesity and medical consequences including diabetes, sleep apnea and cardiac complications. Genotropin is a medication that can improve Katherine's physical health and therefore, is medically necessary.

Medically Necessary means the required extent of health care service, treatment or product that a licensed physician or licensed health care provider (or mandated by state or federal law) would provide to his/her patient for the purpose of diagnosing, palliating or treating a Sickness Illness Disease, or its symptoms. Such health care service, treatment or product must be:

1. in accordance with nationally recognized standards of medical practice and identified as safe, widely used and generally accepted as effective for the proposed use;
2. clinically appropriate in terms of type frequency, intensity, toxicity, extent, setting, and duration;
3. not primarily for the convenience of the patient, physician, or other health care provider; and
4. clearly substantiated by the medical records and documentation concerning the patient's condition;
5. performed in the most cost effective setting required by the patient's condition; and
6. supported by the preponderance of nationally recognized peer review medical literature, if any, published in English language as of date of service.

GH treatment is recommended for the management of PWS in the guidelines of the Lawson Wilkins Pediatric Endocrine Society (LWPES) and the American Association of Clinical Endocrinologists (AACE), the largest organization of practicing endocrinologists in the world.<sup>1,2</sup>

Guidelines published by the AACE and the LWPES recommend a GH dose from 0.24 to 0.35 mg/kg/wk divided into daily doses.<sup>1,2</sup>

Treatment of PWS with GH beginning before age 3 was shown to significantly improve height, growth velocity, and body composition after 1 year of therapy.<sup>3</sup> Children with PWS treated with GH at older ages (mean 9.7 years) for 6 months also had significantly improved height, growth velocity, and body composition.<sup>4</sup>

Studies in adults with PWS have shown that GH continues to have a beneficial effect on body composition without significant side effects.<sup>10</sup>

## Genotropin

Genotropin recombinant GH was approved by the FDA in 2000 and granted orphan drug status as a

safe and effective long-term treatment for growth failure in children with PWS.

Genotropin is a biosynthetic, recombinant human GH that has an identical amino acid sequence to naturally occurring GH made in the pituitary gland.<sup>5</sup> As such, it stimulates linear skeletal growth in patients with PWS.<sup>5</sup> Additional effects of Genotropin include increased protein synthesis, increased muscle mass, reduced fat mass, beneficial effects on lipid metabolism, and alterations in carbohydrate metabolism.<sup>5</sup>

The efficacy and safety of Genotropin for the treatment of children with PWS were demonstrated in 2 randomized, open-label, controlled clinical trials.<sup>5</sup> Patients receiving Genotropin had a significant decrease in fat mass and a significant increase in lean body mass.<sup>5</sup>

Use of Genotropin is supported by a training program that teaches patients how to use the injection device correctly. Genotropin is administered subcutaneously using an injection device that includes 2 separate chambers that facilitate the mixing of the lyophilized GH powder with water.<sup>5</sup> The Genotropin PEN injection system is easy to use and may eliminate waste.

X In summary, growth hormone is a safe and effective therapy for adults with PWS, and is the current medical standard of care for this condition. **We are requesting a reversal of Idaho Medicaid denial based on these current medical standards of care.** If you have further questions regarding this request, please do not hesitate to contact Bruce A. Boston, MD at Children's Hospital, Mail code: CDRCP, 707 S.W. Gaines St., Portland, Oregon 97239-3098. Phone # 503-494-1933 or e-mail: [bostonb@ohsu.edu](mailto:bostonb@ohsu.edu)

Sincerely,  
Kelly Mullholand Behm, BS in Nursing, RN  
Nurse Consultant, Clinical Endocrinology & Research

## References

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## Exhibit: D

# It's not about the height

Allen, TRENDS in Endo & Metab Book Review of Eiholzer book ([PWS. Effects of GH Treatment](#)), May/June 2002

Urs Eiholzer, a prominent investigator of PWS, has recently written a book on PWS which provides an overview of PWS with a special emphasis on GH treatment ([PWS. Effects of GH Treatment](#), Karger, 2001, ISBN: 3805572565). The book was recently reviewed favorably in TRENDS in Endocrinology and Metabolism.

In the book, Eiholzer highlights his impressive 5-year follow-up study of 35 individuals with PWS who were receiving GH treatment. He reports the well-known improvements in growth rate, fat composition, motor development, physical ability and body proportion.

One of the primary issues Eiholzer tackles is the question of whether individuals with PWS are truly lacking in GH, or if they just appear to be lacking GH because obesity can cause GH to decrease. Eiholzer argues that those with PWS indeed have GH deficiency unrelated to their obesity and describes impressive evidence of fasting insulin levels that do not vary depending on whether the subject was obese or not. In addition, he discusses how these levels are very similar to levels of non-PWS obese subjects, providing further support for his argument that those with PWS indeed display a decrease in GH that is unrelated to their weight.

The reviewer notes that one of the parts of the book that is the most fascinating is the photographic documentation of individuals receiving GH treatment. What the reviewer feels was lacking in the book was a discussion of the ethical issues that arise from GH treatment in PWS, including the initial incorrect belief that those with mental disabilities would not benefit from such treatment and were not "entitled" to GH treatment. This is particularly fascinating especially since GH administration in PWS has taught the medical field a tremendous amount about the impressive *non-growth* benefits of this treatment.

Overall, the reviewer feels this is a welcome addition to the literature on PWS and GH administration. The fact that it comes from such a respected specialist makes it a very exciting book especially for geneticists and endocrinologists, but can also be helpful for anyone interested in PWS.

edited: 02/09/2012

source: <http://www.pwsausa.org/GH/GrowthHormoneNotJustHeight.htm>

Medical View

**Growth Hormone for Adults with Prader-Willi Syndrome**

By Barbara Y. Whitman, Ph.D

X Even before all the studies have been completed, the benefits fully examined, and the impact of possible side effects evaluated, growth hormone (GH) replacement therapy has rapidly become standard of care for infants and children with Prader-Willi syndrome (PWS). GH was first approved by the FDA for use in children with PWS in the year 2000. For treated children, the apparent benefits are dramatic and non-trivial; in addition to increased height there is a normalization of cranial proportions and facial features, normalization of hand and foot proportions, and for most, a slim body. With early treatment, most no longer stand out from other children as "different", nor are they readily identifiable as having PWS.

GH replacement for those whose short stature results from congenital, traumatic or surgical endocrine system failures is relatively recent. First utilized in the late 1950s, availability was exceedingly limited, as manufacture required human pituitary glands available only at autopsy. Biosynthetic growth hormone replacements were rushed to market when an excess of those treated with cadaver-derived hormone contracted Creutzfeldt-Jacob disease, a fatal neurodegenerative disorder whose causal mechanisms have only recently been specified. Since the range and depth of studies usually required prior to FDA approval of a drug were incomplete when the use of biosynthetic agents became imperative, a compromise system of surveillance was set up to monitor safety and efficacy — the model currently utilized for many new drug releases.

Short stature has always been considered a characteristic of PWS. Studies indicate that despite normal length and weight at birth, the growth rate in children decelerates over time, so that the average final adult height is approximately two standard deviations below the mean for a non-affected population. That GH deficiencies were the probable basis for the short stature was documented as early as 1971, and subsequent evidence demonstrated the impact of GH on linear growth. In the late 1990s well designed, controlled scientific studies documented that GH therapy resulted in a significantly improved rate of linear growth when compared to those not receiving treatment.

More important, however, was the concomitant improvement in body composition (increased lean, i.e., muscle, mass, increased bone mineral density, and for many, a reduction in the amount of fat tissue); improved metabolism (higher resting energy expenditure, improved respiratory parameters); and increased energy and strength. Self-esteem, behavior, and attention were improved. As the children in those original studies are now reaching adulthood, unpublished data indicate that final adult heights

for individuals treated with GH as children are significantly taller than those not treated.

Unlike most long-term treatments for other chronic conditions, the side effects and safety concerns for GH therapy appear minimal to almost non-existent, in the absence of pre-existing morbid obesity and respiratory compromise. Most clinicians and researchers view the improved body composition and metabolism as far more valuable even than that of increased height.

As a member of one of the first U.S. teams researching GH intervention therapy for youngsters with PWS, I recall seeing the dramatically positive body changes evident at even the first six months' follow-up visit following initiation of GH treatment. I remarked to my colleague on the project, Dr. Susan Myers, "We have to do an adult study to see if we get the same positive body composition effects."

**Growth Hormone Treatment for Adults**

With the advent of puberty, the window of opportunity closes for increasing height through GH intervention due to a "capping" of skeletal growth potential. Further, GH levels normally decline with age in all populations. Entering adulthood already GH deficient presents significant health risks, including osteoporosis, increased body fat, decreased muscle mass, increased risks for heart and vascular disease, fatigue, social isolation and psychological depression. Thus in 1995 the FDA approved GH replacement therapy for those with either childhood or adult-onset GH deficiency. An area of research currently is the use of GH in a geriatric population, often with stunning results.

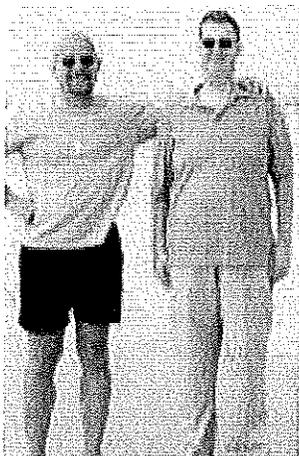
Recent studies indicate that adults with PWS continue to have the same GH deficiency that was present in childhood, with the same health risks attendant to non-PWS, GH-deficient adults. Most adults with PWS also are deficient in sex-steroid/sex hormone production, which further increases the health risks associated with GH deficiency. Thus, in addition to a possible improved body composition, the potential for improved long-term health strongly suggested the need to study GH therapy for adults with PWS.

Dr. Myers and I ultimately joined with several other teams of researchers to conduct a study of GH for 40 adults with PWS, ranging in age from 19 to mid to late 40s. That study and another conducted in Sweden are now completed and results are being published. So what can we understand from these studies at this point?

Significant improvement in body composition is observed in adults with PWS, both males and females, treated with GH replacement therapy. These include increased muscle mass,

## Growth Hormone for Adults with Prader-Willi Syndrome

### Before and After GH Therapy



Top: Al Heinemann with son Matt, who has PWS, just prior to adult GH therapy.

Bottom: Al and Matt in 2005 after a year on adult GH.



with PWS does not yet have full FDA approval, formal demonstration of GH deficiency through provocative GH stimulation testing is required, even for those who have been

and for many, a reduction in fat tissue. There also appears to be a small positive impact on bone mineral density; however, these effects are not as dramatic as those noted in children, probably because bone metabolism does not change as rapidly in adults as it does in children. Loss of fat tissue is particularly apparent in the trunk area, many show a waist and hip body form for the first time. Improvement in energy and strength as demonstrated in such measures as broad jumps, running, and arm curls showed improvement after only one month of treatment. Both attention and cognition showed improvement as well.

Unlike children, however, GH treatment for adults is not without some risk. Increased fluid retention, particularly in the feet and ankles, can initially occur and for some is sufficiently problematic to require discontinuing treatment. For some there may be a negative impact on glucose tolerance, leading to Type II diabetes. For some, the impact on scoliosis must be considered. Thus the risk/benefit ratio must be considered.

### Obtaining GH Treatment for Adults

If a caregiver is considering this treatment for his/her adult with PWS, what is involved? Since GH replacement therapy for adults

on GH for a number of years during childhood. This timed procedure requires injecting a GH stimulating agent while fasting and measuring the peak level of GH secreted into circulating blood at specific points over a specified period of time. However, these procedures are neither straightforward nor simple. There is disagreement on what constitutes deficiency. Depending on the decision-making criteria employed, GH deficiency is defined as peak stimulated GH levels of less than 3-7 ng/ml. While a number of provocative agents are available, peak stimulated levels may differ depending on the agent used, resulting in a requirement for two or more tests. Further complicating the variability related to stimulating agents, variability can exist between analyzing laboratories. Thus, even true GH deficiency can be masked by both the provocative agent used or the analyzing lab employed, resulting in a denial of treatment. In addition, these tests are not without risk, so tolerating two such tests constitutes a major medical procedure. What happens when one test indicates decreased GH levels, while the other is borderline or above the cutoff?

Once GH deficiency is documented, your physician may want to obtain a number of medical tests both prior to initiating therapy and again at least annually as part of therapeutic monitoring. These include an x-ray for scoliosis, a DEXA scan for bone mineral density and body composition, a sleep test to rule out life-threatening (but treatable) apnea, and multiple blood tests, including a fasting lipid panel, fasting glucose, IGF-1, hemoglobin A1c, general chemistry profile with liver enzymes, and thyroid function tests.

### Is It Worth It?

So one may ask, is it worth it? One adult, in her mid-40s when her therapy was started, had shown enormous improvement on a number of physical measures. After 2 years of treatment, she was in danger of losing funding for her medication. She called her insurance company and said, "You can't take away my hormone — my brain is not confused any more!" Her hormone was continued. However, even with appropriate testing and documentation of GH deficiency in adults with and without PWS, obtaining coverage for GH therapy can be difficult in the United States.

Dr. Whitman serves on the PWSA (USA) Scientific Advisory Board. A version of this article including footnotes and list of references is available upon request from our PWSA (USA) national office and in the Members Only section of our website, [www.pwsausa.org](http://www.pwsausa.org).

## Exhibit: F

US National Library of Medicine National Institutes of Health

Growth Horm IGF Res. 2004 Feb;14(1):1-15.

### **Endocrine and metabolic aspects of adult Prader-Willi syndrome with special emphasis on the effect of growth hormone treatment.**

Höybye C.

#### **Source**

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#### **Abstract**

Prader-Willi syndrome (PWS) is a genetic disorder characterized by mild mental retardation, short stature, abnormal body composition, muscular hypotonia and distinctive behavioural features. Excessive eating causes progressive obesity with increased cardiovascular morbidity and mortality. In the PWS genotype loss of one or more normally active paternal genes in region q11-13 on chromosome 15 is seen. It is supposed that the genetic alteration leads to dysfunction of several hypothalamic centres and growth hormone (GH) deficiency (GHD) is common. PWS is well described in children, in whom GH treatment improves body composition, linear growth, physical strength and agility. Few studies have focused on adults. We examined a cohort of 19 young adults with clinical PWS (13 with positive genotype) and mean BMI of 35 kg/m<sup>2</sup>. At baseline the activity of the GH-insulin-like growth factor-I (IGF-I) system was impaired with low GH values, low total IGF-I and in relation to the obesity low levels of free IGF-I and non-suppressed IGF-binding-protein-1 (IGFBP-1). 2/3 were hypogonadal. Bone mineral density (BMD) was low. Four patients had impaired glucose tolerance and nine patients high homeostasis model assessment (HOMA) index, indicating insulin resistance. Seven patients had a moderate dyslipidemia. The 13 patients with the PWS genotype were shorter and had significantly lower IGF-I. Seventeen (9 men and 8 women), subsequently completed a 12 months GH treatment trial, and GH had beneficial effects on body composition without significant adverse effects. The effects were more pronounced in the patients with the PWS genotype. Analysis of peptides involved in appetite regulation showed that leptin levels were high reflecting obesity and as a consequence NPY levels were low. In relation to the patients obesity circulating oxytocin levels were abnormally low and ghrelin levels abnormally high. Thus, oxytocin and ghrelin might be involved in the hyperphagia. NPY, leptin and ghrelin did not change during GH treatment. In conclusion this pilot study showed that adults with PWS have a partial GH deficiency, and GH treatment has beneficial effects on body composition in adult PWS without significant side-effects. Larger and longer term studies on the effect of GH replacement in adult PWS are encouraged.

PMID:14700552 [PubMed - indexed for MEDLINE]

source: <http://www.ncbi.nlm.nih.gov/pubmed/14700552>

**Exhibit: G****EJ754593 - *Quality of Life and Psychological Well-Being in GH-Treated, Adult PWS Patients: A Longitudinal Study***

**ERIC #:** EJ754593

**Title:** Quality of Life and Psychological Well-Being in GH-Treated, Adult PWS Patients: A Longitudinal Study

**Authors:** Bertella, L.; Mori, I.; Grugni, G.; Pignatti, R.; Ceriani, F.; Molinari, E.; Ceccarelli, A.; Sartorio, A.; Vettor, R.; Semenza, C.

**Source:** Journal of Intellectual Disability Research, v51 n4 p302-311 Apr 2007

**Peer Reviewed:** Yes

**Publisher:** Blackwell Publishing. 350 Main Street, Malden, MA 02148. Tel: 800-835-6770; Tel: 781-388-8599; Fax: 781-388-8232; e-mail: customerservices@blackwellpublishing.com; Web site: [http://www.blackwellpublishing.com/jnl\\_default.asp](http://www.blackwellpublishing.com/jnl_default.asp)

**Publication Date:** 2007-04-00

**Pages:** 10

**Pub Types:** Journal Articles; Reports - Research

**Abstract:** Background: Prader-Willi syndrome (PWS) is a congenital alteration of chromosome pair 15. It is characterized by short stature, muscular hypotonia, hyperphagia, obesity, behavioural and emotional disturbances, hypogonadism and partial Growth Hormone (GH) deficiency. The aim of this study was to assess the long-term effect of GH treatment on the psychological well-being and Quality of Life (QoL) in an adult PWS group. Methods: A total of 13 PWS patients, their diagnosis confirmed by genetic tests, and their parents were recruited for this study. The participants were administered the 36-Items Short Form Health Survey (SF-36) and the Psychological General Well-Being Index (PGWBI), for the assessment of QoL and psychological well-being, at the beginning of GH treatment, and at following intervals of 6, 12 and 24 months. Modified versions of the same questionnaires were given to the parents. Results: Significant improvement with respect to the baseline was found, on both scales, in the evaluation of both physical and psychological well-being, although the parents evaluation was less optimistic than that of the patients. Conclusion: Our findings suggest that the amelioration of QoL and psychological status is sustained in patients who continue GH treatment.

**Abstractor:** Author

**Exhibit: H*****EJ686388 - Cognitive, Emotional, Physical and Social Effects of Growth Hormone Treatment in Adults with Prader-Willi Syndrome*****Authors:** Hoybye, C; Thoren, M.; Bohm, B.**Source:** Journal of Intellectual Disability Research, v49 n4 p245-252 Apr 2005**Peer Reviewed:** Yes**Publisher:** Journal Customer Services, Blackwell Publishing, 350 Main Street, Malden, MA 02148. Tel: 800-835-6770 (Toll Free); Fax: 781-388-8232; e-mail: [subscrip@bos.blackwellpublishing.com](mailto:subscrip@bos.blackwellpublishing.com).**Publication Date:** 2005-04-00**Pages:** 8**Pub Types:** Journal Articles; Reports - Research; Tests/Questionnaires

**Abstract:** Prader-Willi syndrome (PWS) is a multisystem genetic disorder characterized by short stature, muscular hypotonia, hyperphagia, obesity, maladaptive behaviour, hypogonadism and partial growth hormone (GH) deficiency (GHD). Severe GHD of other aetiologies has been shown to affect mood and quality of life negatively, and there are reports of improvements with GH replacement. We have studied cognitive, emotional, physical and social parameters in PWS adults at baseline, during and after GH treatment. Patients and methods Nineteen patients, 9 females and 10 males, median age 25 years, mean BMI 35 kgm<sup>2</sup> participated in this study. Approximately half of the group had GHD. All patients fulfilled the clinical criteria for PWS and 13 had a positive genotype. The patients were randomized to 6 months of treatment with either GH 1.6 IU/day (0.53 mg/day) or placebo, followed by 12 months of active GH treatment. Treatment was then stopped, and the patients were followed for an additional period of 6 months. A test battery for general cognitive evaluation and a computer-based measurement of reaction time, motor speed and fluency were employed at baseline, after 6 months and at the end of GH treatment. At the same time intervals, a self-evaluation questionnaire was answered at the end of each test session. Other questionnaires reflecting the patients cognitive, emotional, physical and social status were answered by relatives caretakers at baseline and at 3 and 6 months following cessation of GH treatment. Baseline cognitive level was estimated to be moderately to mildly impaired; IQ range was 40-90. The results from some of the cognitive and the motor performance tests improved significantly after 6 and 18 months of GH treatment. According to the questionnaires, both the patients and the relatives caretakers evaluated physical status rather negatively at baseline, but still, impairments in both physical and social status and overall functioning were observed when GH treatment was discontinued. The self-evaluation did not change in any aspect during GH treatment. In this pilot study of an adult PWS cohort, we were able to document beneficial effects in mental speed and flexibility and in motor performance during GH treatment. Impairment was seen in physical and social status as well as overall functioning, when GH treatment stopped. Studies of larger cohorts are needed to further elucidate the role of GH treatment in this group of patients.

**Exhibit: I**

## **Long-Term Growth Hormone Therapy Changes the Natural History of Body**

### **Composition and Motor Function in Children with Prader-Willi Syndrome**

Aaron L. Carrel, Susan E. Myers, Barbara Y. Whitman, Jens Eickhoff and David B. Allen, Department of Pediatrics, University of Wisconsin American Family Children's Hospital, Madison, Wisconsin; Department of Pediatrics, Cardinal Glennon Children's Medical Center, St. Louis, Missouri; and Colorado State University, Ft. Collins, Colorado

To assess the impact of hGH therapy begun early in life on the natural history of PWS, comparisons were made of height, body composition, and strength in similar-age children with PWS who had never been treated with hGH with those with PWS treated with hGH for 6 years.

Forty-eight children with PWS were studied: 21 subjects aged 6–9 years who had been treated with hGH for 6 years beginning at 4–32 months were compared with 27 children aged 5-9 years prior to treatment with hGH. Percent body fat, lean body mass, carbohydrate/lipid metabolism, and motor strength were compared.

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.

[Note: For more detailed information, see *The Journal of Clinical Endocrinology & Metabolism* Vol. 95, No. 3 1131-1136, 2010]

edited: 02/09/2012

source: <http://www.pwsausa.org/GH/USALong-TermGHStudy.htm>

**Exhibit: J**

**INTERNATIONAL PRADER-WILLI SYNDROME ORGANISATION  
7<sup>TH</sup> SCIENTIFIC CONFERENCE**

**MAY 20-21, 2010, TAIPEI, TAIWAN**

**TWO YEAR OF GROWTH HORMONE THERAPY IMPROVES BODY COMPOSITION IN ADULTS WITH  
PRADER-WILLI SYNDROME**

Rasmus Sode-Carlson<sup>1</sup>, Jens Bollerslev<sup>2</sup>, Thomas Schreiner<sup>2</sup>, Jens Sandahl Christiansen<sup>3</sup>, Stense Farholt<sup>1</sup>, Kai Fr. Rabben<sup>4</sup>, Charlotte Höybye<sup>5</sup>

**INTRODUCTION:** Prader-Willi syndrome (PWS) presents clinically with a multitude of findings, including abnormal body composition and partial growth hormone (GH) deficiency. Until now three studies have reported beneficial effects upon body composition of GH treatment in adults with PWS. However, only one of these studies had the optimal randomised controlled design.

**AIM:** The aim of this study was to confirm and substantiate the results from previous studies.

**PATIENTS AND METHODS:** 46 patients, 25 women, 21 men, age 29 years (16-41) (median and range) with genetically verified PWS participated in a multinational Scandinavian study. The patients were randomised to treatment with GH or placebo for 12 months, 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. The study was approved by the local Ethical Committees.

**CONCLUSION:** 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 years results, findings persist during long-term therapy.

edited: 02/09/2012

source: <http://www.pwsausa.org/GH/GrowthHormoneBodyComp.htm>

Exhibit: K

# How Much of the Phenotype of Prader-Willi Syndrome is due to Growth Hormone Deficiency?

Suzanne B. Cassidy<sup>1</sup>, Ellen Simpson<sup>1</sup>, Shauna Heeger<sup>2</sup>

<sup>1</sup>Division of Human Genetics, Department of Pediatrics, University of California, Irvine, 101 The City Drive, Bldg 2, Orange, CA 92868, (714) 456-6261, and <sup>2</sup>Case Western Reserve University.

The classical physical phenotype of Prader-Willi syndrome (PWS) is most notable for hypotonia, characteristic facial appearance (narrow bifrontal diameter, almond-shaped and sometimes upslanting palpebral fissures, downturned mouth), short stature, central obesity, small hands and feet, genu valgus, decreased muscle mass causing characteristic body habitus, straight ulnar borders and straight calf borders, and hypoplastic genitalia. In recent years, the short stature has been associated with growth hormone deficiency (hGH), as has altered body composition. PWS is now an FDA approved indication for the use of hGH, and it is becoming standard of care. Most newly diagnosed individuals are being treated from the time of diagnosis or shortly thereafter, which is often infancy. Observation of treated patients has suggested a significant impact on physical phenotype.

In the general population, growth hormone deficiency causes not only short stature, but also hypotonia, decreased muscle mass and increased fat mass (i.e., altered body composition), central obesity, osteopenia, small hands and feet, delayed bone age, and low IGF-1. All of these are present in PWS. Reports based on recent double-blind crossover studies of hGH treatment in PWS have indicated dramatic increase in growth rate (especially in the first year of treatment) and a variety of other effects, including: 1) improved body composition (higher muscle mass, lower fat mass), 2) improved weight management; 3) increased energy and physical activity; 4) improved strength, agility and endurance; and 5) increased respiratory muscle forces. These studies have also shown no adverse effects on behavior, and in fact suggest improvement in depression.

We have been conducting an ongoing detailed multi-system standardized phenotypic evaluation of individuals with PWS over the past several years for the purpose of genotype-phenotype comparison. Given the recent shift to hGH treatment, recently enrolled patients with hGH replacement can be compared phenotypically to earlier enrolled patients, who were not hGH treated. These comparisons, as well as review of patients followed in a multi-disciplinary PWS management clinic and of studies by others, indicate a number of effects on physical phenotype. Such effects include changes toward normal in body habitus, limb form, hand & foot length, facial appearance, bone density, body composition, and genital size. These changes are most impressive if hGH is started within the first year of life.

These impressive effects from replacement of a single hormone raise interesting questions about the relative importance of genetic alterations in causing at least this one dysmorphic syndrome.

edited: 02/09/2012

source: <http://www.pwsausa.org/GH/PhenotypePWSduetoGH.htm>

Exhibit: L

Office Visit-  
Transcribed

Katherine Marie Jenkins (MR# 01906760)

Transcription	Type	ID	Date	Author
	Progress Note	8896470000003200507300838		
Authenticated by OTHER, FACULTY on 3/4/2005				
Document Text				
		00004213414HP1063E 01906760 JENKINS	03/04/200503/04/200503/04/2005 4462340	KATHERINE M

Referred From and Faxed To:

Referred To: Bruce Boston, M.D.

Consulting Physician: Bruce Boston, M.D.

Consultation Date: 03/04/2005

PEDIATRIC ENDOCRINOLOGY CLINIC

History: We are seeing this 8-4/12-year-old girl in the Pediatric Endocrinology Clinic in consultation for evaluation of Prader-Willi syndrome and growth hormone replacement therapy for that condition.

Katherine (Katie) is accompanied today by her mother and father who have driven 8 hours from Idaho for this appointment today. They describe classic features of a Prader-Willi syndrome in Katie who was diagnosed with this syndrome in her first month of her birth what sounds to have been a FISH probe genetic study showing a microdeletion, though they are not sure about the specifics of the diagnostic tests, and we do not have any reports of that reported genetic testing.

Katie's birth weight was 5.5 pounds, presented in breech fashion, vaginally delivered, stayed in the hospital for the first month of life because she was quite "floppy" and had difficulty feeding requiring a gastrostomy tube placement.

She had some delayed development specifically in regards to speech requiring speech therapy for enunciation, learnt to walk around 18 months, had scoliosis detected at an early age requiring a brace placement, manufactured at the Shriners Hospital here on the ORSU's campus.

Around age 3 or 4, she developed hyperphagia, to a point that the parents have had to lock the fridge and put away foods at heights unreachable by her. Even at school, they have had to make sure that her access to food is quite restricted, and they have managed to keep her weight at the 75th percentile though the mother is concerned that even though there have been no dietary changes, she seems to be gaining weight more easily as of late.

Social History: They describe that she has had a good social interaction with her peers but describes her as throwing temper tantrums and being obsessive compulsive. She was kept back years, she is in first grade right now. She enjoys playing in school.

Family History: She has 4 siblings aging in range 16 to 26 years old. Mother describes that all her children, though none of the other ones have Prader-Willi syndrome, are short in stature (shorter than what we would expect from predicted final growth height based on parent's height). Mother has polycystic ovarian syndrome. No other familial disorders.

Past Medical History: Katie has besides diagnosis of Prader-Willi, she has scoliosis, strabismus, and recently had a nasal fracture when she sustained injury to her face playing soccer.

Review of Systems: No obstructive sleep apnea symptoms such as observed apnea, daytime somnolence, or loud snoring. No wheezing or asthma. No

Encounter Date: 03/04/2005

abdominal pain, constipation, or recurrent diarrhea. Her mother has been concerned because of increased weight gain despite no dietary changes and very careful monitoring of food intake. No arthralgias or muscle pain. No pubic or axillary hair development, breast development, or body odor.

Physical Examination: Vital Signs: Height 114.3 cm that places her below the 5th percentile, weighing 29.4 kg places her right below the 75th percentile, blood pressure is 94/57, and pulse of 98. General: Katie is a comfortable, gregarious girl in no distress. She has subtle bitemporal indentations, subtle almond-shaped palpebral fissures, somewhat short fingers in relation to her palm, and puffiness over the dorsum of her hand. Cardiovascular: Unremarkable. Abdomen: Notable for gastrostomy tube scarring. No abdominal masses are palpated. No evidence of axillary hair or breasts development. Surprisingly in the evaluation of scoliosis, there is no obvious spinal scoliosis when she is bending at her brace.

Assessment and Plan: An 8-4/12-year-old with history of Prader-Willi syndrome. Given the salient features of hypotonia at birth, hyperphagia, associated conditions are strabismus and scoliosis and reported history of positive genetic studies, though we do not have actual report of that genetic study.

In addition given the short height of her siblings which is shorter than what will be expected from predicted height based on parent's height, there maybe a short stature gene in this family which Katie may or may not have inherited.

Understandably, Katie's parents are concerned about her growth, and we will do a bone age today to ascertain what her bone age is. We discussed treatment with the growth hormone explaining that GH not only increases height velocity but improves body composition, increases muscle mass/strength and may improve obstructive sleep apnea. We, however, mentioned the rare case reports of sudden death in Prader-Willi kids having been given growth hormone, and we believe this may be due to this sudden death occurring in those with untreated obstructive sleep apnea.

We also cautioned that rapid growth from any cause be it puberty or growth hormone administration may worsen scoliosis.

Because of this, she will require a sleep study to rule out obstructive sleep apnea, and if she does not have sleep apnea and her pediatric orthopedic surgeon would be comfortable with the institution of growth hormones, then we could pursue a growth hormone replacement therapy.

In addition, Katie's parents expressed interest in Katie participating in Dr. Boston's Prader-Willi Syndrome Study and Dr. Bishop, another Pediatric Endocrinology Fellow, will contact Katie's family to see if it would be feasible to have Katie enroll in the study given the distance they may have to travel.

Followup will be set up at 6 months at this point.

Ali Bahar, M.D.

Bruce Boston M.D.

AB / HB  
3289541 / 403980 / 36688 / 31183  
D: 03/04/2005  
T: 03/05/2005

cc: