

## Growth Hormone Research Society Workshop Summary: Consensus Guidelines for Recombinant Human Growth Hormone Therapy in Prader-Willi Syndrome

Cheri L Deal,<sup>1</sup> Michèle Tony<sup>2</sup>, Charlotte Höybye<sup>3</sup>, David B. Allen<sup>4</sup>,  
Maïthé Tauber<sup>5</sup>, Jens Sandahl Christiansen<sup>6</sup>, and  
the 2011 GH in PWS Clinical Care Guidelines Workshop Participants.<sup>a</sup>

Research Center and Department of Pediatrics<sup>1</sup>, CHU-Sainte-Justine and Department of Public Health<sup>2</sup>,  
Université de Montréal, Montréal, Canada; Department of Endocrinology, Metabolism and Diabetes<sup>3</sup>,  
Karolinska University Hospital, Stockholm, Sweden; Department of Pediatrics, University of Wisconsin  
School of Medicine and Public Health<sup>4</sup>, Madison, WI; Department of Endocrinology, Hôpital des Enfants  
and Université Paul Sabatier<sup>5</sup>, Toulouse, France; Department of Endocrinology and Diabetes<sup>6</sup>, Aarhus  
University Hospital, Aarhus, Denmark

**Context:** rhGH therapy in Prader-Willi syndrome (PWS) has been used by the medical community and advocated by parental support groups since its approval in the US in 2000 and in Europe in 2001. Its use in PWS represents a unique therapeutic challenge which includes treating individuals with cognitive disability, varied therapeutic goals that are not focused exclusively on increased height, and concerns about potential life-threatening adverse events.

**Objective:** To formulate recommendations for the use of rhGH in children and adult patients with PWS.

**Evidence:** A systematic review of the clinical evidence in the pediatric population, including randomized controlled trials (RCTs), comparative observational studies and long term studies (>3.5 years). Adult studies included RCTs of rhGH treatment for [mteq] 6 months and uncontrolled trials. Safety data were obtained from case reports, clinical trials and pharmaceutical registries.

**Methodology:** Forty-three international experts and stakeholders followed clinical practice guideline development recommendations outlined by the AGREE Collaboration ([www.agreetrust.org](http://www.agreetrust.org)). Evidence was synthesized and graded using a comprehensive multicriteria methodology (EVIDEM) ([www.evidem.org/praderwilli](http://www.evidem.org/praderwilli)).

**Conclusions:** Following a multi-disciplinary evaluation preferably by experts, rhGH treatment should be considered for patients with genetically-confirmed PWS in conjunction with dietary, environmental and lifestyle interventions. Cognitive impairment should not be a barrier to treatment, and informed consent/assent should include benefit/risk information. Exclusion criteria should include severe obesity, uncontrolled diabetes mellitus, untreated severe obstructive sleep apnea, active cancer or psychosis. Clinical outcome priorities should vary depending upon age and the presence of physical, mental and social disability, and treatment should be continued for as long as demonstrated benefits outweigh the risks.

**P**rader-Willi syndrome (PWS) is a rare genetic disorder (OMIM: #176270) characterized by hypotonia, poor feeding in infancy, hyperphagia with evolving obe-

sity, hypogonadism, decreased adult height, and cognitive and behavioral disabilities (1, 2).

The birth incidence of PWS is difficult to ascertain, but data from several studies suggest that it is at least 1 in

25,000 live births. PWS is genetically heterogeneous; in approximately 65%–70% of patients PWS results from a deletion of the paternally inherited chromosomal 15q11.2–q13 region (DEL15), 25–30% from maternal uniparental disomy for chromosome 15 (UPD15), while ~1% have imprinting defects (ID) or translocations involving chromosome 15 (2, 3).

The therapeutic rationale for use of recombinant human growth hormone (hGH) (rhGH) is derived from our understanding of the comorbidities seen in PWS, which resemble those seen in association with growth hormone (GH) deficiency (GHD) (e.g., reduced muscle strength, altered body composition, low energy expenditure and reduced growth even in the presence of obesity). Although the etiology of impaired GH secretion in PWS remains controversial due to the common occurrence of obesity, the serum levels of IGF-I are reduced in most children (4–6) and adults (7) with PWS, and excess body fat is seen in even nonobese affected children (8, 9). Reduced GH responses to a variety of GH secretagogues, as well as decreased 24-h spontaneous GH release, have been documented in 58%–100% of affected children (10). Information regarding GH secretory pattern in adult patients with PWS is more limited, and suggests more variability, with many potential explanations (7, 11–13).

Short-term rhGH treatment of children with PWS was first reported in 1987 (14). It has been used by many members of the international medical community and advocated by parental support groups since its FDA approval in 2000 for use in children with PWS, based on short term growth data and subsequently for its effects on body composition. However, the use of rhGH therapy for this condition represents a unique therapeutic challenge which includes treating individuals with cognitive disability, varied therapeutic goals that are not focused exclusively on increased height, (15), and concerns about potential life-threatening adverse events (16).

Prior expert consensus documents discuss the general care of patients with PWS, including some discussion of rhGH therapy in children and adults with PWS, (17, 18) although many questions remained, particularly the effects on functional outcome and on long-term body composition changes. Recent pertinent publications have since appeared, (19–29) and the Growth Hormone Research Society therefore held a Consensus Workshop in order to systematically review the literature and grade the available evidence (30, 31) and provide concise recommendations for the use of rhGH in this context with adherence to The Principle of Respect for Persons (32) as the guiding ethical

principle for rhGH use in PWS (i.e., provision of care and protection of patients who do not have autonomy).

The objective of the workshop was to evaluate the effects of rhGH therapy in pediatric and adult patients with PWS and provide evidence-based guidelines for its use, summarized herein.

### Workshop Methodology

Forty-three experts (pediatric and adult endocrinologists, clinical and basic geneticists, epidemiologists, a nutrition specialist, an orthopedic surgeon, a psychiatrist, health technology assessment (HTA) specialists, a bioethicist, health economist, and a patient advocate) participated by invitation from the scientific committee (see author list). Clinical representatives from 5 manufacturers of rhGH also submitted their PWS-specific safety data.

Prior to the workshop, an extensive literature review based on a multicriteria methodology (30, 31) was performed to identify relevant available data concerning rhGH treatment for patients with PWS. For clinical evidence in the pediatric population, RCTs, (20–26, 33–41) comparative observational studies (42–48) and long term studies (>3.5 y) (5, 49–58) were included. Adult studies included RCTs of rhGH treatment for [mteq] 6 mo (7, 29, 59, 60) and uncontrolled trials, (61–64) since data were more limited. Safety data from pharmaceutical registries (phase 4 trials) (1) and sponsored clinical trials (phase 3) were reviewed. Data on disease, therapeutic context, and economic, ethical and societal aspects were also included to reflect a broad international context. Details on approach, evidence tables and data summaries are available in **Supp Table 1a,b** and on the workshop website (65).

Level of evidence was evaluated using the scoring procedure based on the Oxford Centre for Evidence-based Medicine (CEBM) Level of Evidence scale (66). (**Supp Table 1c**) Strength of evidence was graded independently by two of the authors (CD and MT) using the EVIDEM Quality Assessment (QA) instrument, (30, 67) and a quality grade on a 4-point scale (low to excellent) was then assigned to each publication. In the rare cases of disagreement, the study was re-examined jointly.

Synthesized information by criteria was then provided to workshop participants prior to the workshop discussions for i) validation of content, and ii) to provide background information to answer relevant questions concerning GH and PWS (**Supp Table 2**).

Based on 2 d of structured talks and breakout sessions, participants formulated and categorized levels of recommendations using the following system:

Abbreviations:

A: Evidence or general agreement that a given procedure of treatment is beneficial, useful and effective

B: Weight of evidence is in favor of usefulness or efficacy

C: Usefulness or efficacy is less well established by evidence or opinion

D: Evidence or general agreement that the procedure or treatment is not useful or effective and in some cases may be harmful.

To each recommendation, a CEBM level of evidence score was assigned to reflect the origins of the data which lead to the recommendation.

### Overview of Evidence Quality

Multiple pediatric RCTs with rhGH have reported statistically significant effects in patients with PWS on growth, body composition, resting energy expenditure, motor development (infants and children), muscle strength, exercise tolerance, bone health and lipid profiles. (20–26, 33–41, 50) Overall, these trials have been performed in small populations and durations were short compared to the length of rhGH treatment in the real life setting; quality grade ranged from low (10 publications) to high (1 publication). There is only one placebo-controlled study (35) and one controlled dose-response study (34) in the pediatric population, although the adult trials include placebo-controlled groups (7, 29, 59, 60). Most patients had genetically-confirmed diagnoses. Methodological issues were noted in several studies including incomplete reporting of patient numbers, lack of discussion of randomization methods, rare inclusion of intent-to-treat analyses, limited statistical details (*P*-values only), and minimal information about important confounders (e.g., socio-economic status, degree of adherence to diet, exercise plan). Only 2 studies reported individual patient responses (26, 33).

It is difficult to criticize the validity of these studies based on flawed methodologies, since the effects are consistent at least in the short term (1 y data), as demonstrated by recent meta-analyses in children and adults (19, 28). There are data regarding clear benefits to rhGH treatment in infants, childhood, adolescence, transition to adulthood, and in young adulthood, but there are less long-term data available after the fourth decade.

### Summary of Recommendations

The workshop participants established 15 recommendations dealing with rhGH use in PWS, as shown in Table 1.

Considerations specific to each recommendations are discussed in a companion review (68) and are briefly summarized here.

### Baseline evaluation of the GH-IGF Axis before rhGH treatment

Previous expert opinions (17) have suggested that GH testing is not necessary in children with PWS, although some countries require it in order for treatment reimbursement. It was agreed that over 50% of infants and children with PWS are, or will become GH deficient by standard testing protocols (4, 10, 26, 38, 50, 69–73). No consensus was reached concerning the frequency of testing in cases where GH sufficiency is initially documented. Determining the presence of GHD after attainment of adult height may be beneficial, however, since reports from dynamic testing in adults suggest that GHD is not universal, and many countries require testing prior to treatment of adults with GHD (28). It is not known if GH secretory status predicts metabolic response to rhGH treatment. Furthermore, within a research context, and in order to increase our understanding of genotype-phenotype relationships, GH testing may be desirable. Since serum IGF-I is a useful biomarker for monitoring compliance with treatment as well as sensitivity to GH, all participants agreed that baseline IGF-I levels should be determined.

### Additional considerations prior to starting rhGH treatment

All participants agreed that evaluation of patients prior to beginning treatment should ideally include a complete assessment coordinated by a multidisciplinary team with expertise in PWS, and summarized in Table 2. This stems from the importance of diagnosing and treating comorbidities that may impact on GH safety as well as on GH response.

Product labeling information for all of the rhGH preparations commercially available (regardless of approved diagnosis) lists several contraindications to rhGH use, including acute critical illness, severe obesity or severe respiratory impairment, active malignancy, active proliferative or severe nonproliferative diabetic retinopathy, and hypersensitivity to the product. Workshop participants acknowledged these exclusion criteria and felt that active psychosis should also be included. Psychiatric illness is now increasingly recognized in patients with PWS (74).

Careful attention should be given to the clinical criteria used to define severe pediatric obesity, since there are no clear definitions as in adults ( $BMI > 40 \text{ kg/m}^2$ ). Workshop participants felt it prudent to consider obesity in the pediatric population with PWS as “severe” if a child with a BMI over the 95th percentile manifests complications of obesity such as sleep apnea, nonalcoholic fatty liver disease, or abnormalities of carbohydrate metabolism. Since treatment with rhGH decreases insulin sensitivity, uncontrolled diabetes mellitus, regardless of the presence or ab-

**Table 1.** Summary of Clinical Care Guidelines for rhGH Therapy in PWS

- I. After genetic confirmation of the diagnosis of PWS, rhGH treatment should be considered and, if initiated, continued for as long as demonstrated benefits outweigh the risks. (Recommendation level A; level of evidence 1)**
- II. GH stimulation testing should not be required as part of the therapeutic decision-making process in infants and children with PWS. (Level of recommendation A; level of evidence 3)
- III. Adults with PWS should have an evaluation of the GH/IGF axis prior to rhGH treatment. (Recommendation level A; level of evidence 4)
- IV. Prior to initiation of rhGH therapy, patients with PWS should have a genetically confirmed diagnosis and expert multi-disciplinary evaluation. (Recommendation level A; level of evidence 5)
- V. *Exclusion criteria for starting rhGH in patients with PWS include severe obesity, uncontrolled diabetes, untreated severe obstructive sleep apnea, active cancer and active psychosis. (Recommendation level A; level of evidence 4)*
- VI. *Scoliosis should not be considered a contraindication to rhGH treatment in patients with PWS. (Recommendation level A; level of evidence 2)*
- VII. Infants and children with PWS should start with a daily dose of 0.5 mg/m<sup>2</sup>/day subcutaneously with subsequent adjustments toward 1.0 mg/m<sup>2</sup>/day every 3–6 months according to clinical response\* and guided by maintenance of physiologic levels of IGF-I\*\*. (Recommendation level A; level of evidence \*1, \*\*5)
- VIII. Adults with PWS should receive a starting dose of 0.1–0.2 mg/day based on age, presence of edema, prior rhGH exposure and sensitivity, and concomitant oral estrogen use. Subsequent dosage titration should be based on clinical response, age, and sex appropriate IGF-I levels in the 0 to +2 SD range. (Recommendation level A; level of evidence 2)
- IX. Selection of patients with PWS for rhGH therapy and dosing strategy should not depend on the genetic class of PWS (DEL15; UPD15; ID). (Recommendation level A; level of evidence 2)
- X. IGF-I levels in patients with PWS on rhGH treatment should be maintained within the upper part of normal range (+1 to +2 SDS) for healthy, age-matched normal individuals. (Recommendation level B, level of evidence 3 (adults), 5 (children))
- XI. Clinical outcome priorities should vary depending on the age, and on the presence of physical, mental, and social disability. (Recommendation level A; level of evidence 1)
- XII. Monitoring of GH treatment in patients with PWS should address specific benefits and risks of treatment in this population and the potential impact of other hormonal deficiencies. (Recommendation level A; level of evidence 3)
- XIII. Patients with PWS receiving GH must be followed carefully for potential adverse effects during GH treatment. (Recommendation level A; level of evidence 1)
- XIV. Treatment with GH must be in the context of appropriate dietary, environmental, and lifestyle interventions necessary for care of all patients with PWS. (Recommendation level A; level of evidence 4)
- XV. Cognitive impairment should not be a barrier to treatment with GH for patients with PWS. (Recommendation level A; level of evidence 4)

**Recommendation levels:** A, Evidence or general agreement that a given procedure of treatment is beneficial, useful and effective; B, Weight of evidence is in favor of usefulness or efficacy; C, Usefulness or efficacy is less well established by evidence or opinion; D, Evidence or general agreement that the procedure or treatment is not useful or effective and in some cases may be harmful. **Levels of evidence:** 1, Systematic review of randomized trials; 2, Randomized trial or observational study with dramatic effect; 3, Non-randomized controlled trial/follow-up study; 4, Case-series, case-control or historically controlled studies; 5, Mechanism-based reasoning

sence of diabetic complications such as retinopathy, demands attention *prior* to initiation of rhGH therapy in patients with PWS (104).

Children with PWS have a high incidence of both central apnea and obstructive apnea (75–77). Marked obesity or intercurrent respiratory tract infection (often underdiagnosed because of the absence of fever), can exacerbate obstructive apnea and may even lead to sudden death (78–82). Since rhGH therapy can theoretically lead to lymphoid tissue growth in children due to increased IGF-I effects (100) patients and parents must be fully informed about the potential association between rhGH therapy and unexpected death during the pretreatment consenting process, and polysomnography should be performed before starting therapy. rhGH therapy is contraindicated in children with breathing difficulties until ENT surgery and treatment of respiratory-compromising obesity has been achieved. Therapy should not be initiated during an acute respiratory infection, but it need not be interrupted during

subsequent episodes of respiratory infection unless indicated because of onset of breathing difficulties.

Scoliosis in PWS is not a contraindication to rhGH treatment; its occurrence is common (up to 30%–80% depending on age), but neither its incidence nor its rate of progression are influenced by rhGH therapy (21).

The potential role of the GH-IGF axis in cancer incidence and/or progression has received a great deal of recent attention (83) despite the safety record, to date, of rhGH treatment. The recent SAGhE publications do not specifically address rhGH use in patients with PWS, and a true appreciation of dose-related risks of rhGH will require better and longer surveillance protocols, since all observational studies are subject to bias (84, 85). (86, 87)

The potential development of central adrenal failure, which may not be clinically relevant except during intercurrent illness and/or surgical intervention, was also discussed. Investigations have not uniformly documented a high incidence of central adrenal failure in PWS (88–90).

**Table 2.** Multi-disciplinary Evaluation of Pediatric and Adult Patients with PWS Before Starting rhGH Treatment<sup>a</sup>

Evaluation	Testing/Interventions
<ul style="list-style-type: none"> <li>● Endocrine examination to document anthropomorphic status: weight, length/height, BMI (and if possible, waist circumference and skinfold thickness), pubertal status and presence of additional endocrine deficiencies</li> </ul>	<ul style="list-style-type: none"> <li>● Bone age determination in infants and children</li> <li>● Evaluation of hypothyroidism (TSH, free T4, free T3) and commencement of replacement if appropriate</li> <li>● Determination of IGF-I level and, if possible, GH response to provocative testing particularly in adult individuals</li> <li>● Evaluation of metabolic status if age [mteq] 12 y and obesity: HbA1c, fasting insulin and glucose; consider oral glucose tolerance test (OGTT) if family history of diabetes, acanthosis nigricans or ethnic risk factors</li> <li>● Evaluation of cardiovascular risk profile as per guidelines for obese individuals:<sup>b</sup> fasting total cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol</li> <li>● Assess for hepatic steatosis as per guidelines for obese individuals:<sup>b</sup> AST and ALT levels, abdominal ultrasound and biopsy where appropriate</li> <li>● Body composition evaluation if available (Dual-energy x-ray photon absorptiometry or bioelectrical impedance)</li> <li>● Consider need for evaluation of adrenal function on an individual basis</li> <li>● DNA studies to confirm PWS</li> <li>● Nutritional evaluation and advice including use of food diary, control of food environment, diet composition and caloric intake</li> <li>● Age-appropriate psychomotor testing</li> <li>● Physiotherapy and Occupational Therapy referral</li> <li>● Tonsillectomy and adenoidectomy where indicated</li> <li>● Sleep oxymetry is mandatory prior to starting rhGH in all patients, preferably completed by polysomnographic evaluation</li> <li>● Spine x-ray</li> <li>● Procurement of legal guardian consent and patient assent/consent according to age and cognitive status</li> </ul>
<ul style="list-style-type: none"> <li>● Genetic evaluation and counseling</li> <li>● Referral to dietician</li> </ul>	
<ul style="list-style-type: none"> <li>● Assessment of developmental and cognitive status</li> <li>● Assessment of motor function if possible</li> </ul>	
<ul style="list-style-type: none"> <li>● ENT referral if history of sleep-disordered breathing, snoring, or enlarged tonsils and adenoids are present</li> <li>● Referral to Pneumologist/Sleep Clinic</li> </ul>	
<ul style="list-style-type: none"> <li>● Scoliosis evaluation and referral to orthopedic surgeon if indicated</li> <li>● Family instruction on rhGH treatment including benefits and risks of the treatment and importance of careful monitoring</li> </ul>	

<sup>a</sup>Adapted and modified from: Goldstone AP, Holland AJ, Hauffa BP, Hokken-Koelega AC, Tauber M. Recommendations for the diagnosis and management of Prader-Willi syndrome. *J Clin Endocrinol Metab.* 2008;93(11):p 4188.(17)

<sup>b</sup>For guideline references in obesity, see Lau *et al.*, 2007(128), August *et al.*, 2008(129) and Australian Government Department of Health and Ageing, 2009(130)

No consensus was reached concerning the need for adrenal axis testing prior to initiation of rhGH, but families and clinicians should remain vigilant and not hesitate to use stress doses of glucocorticoids as clinically indicated.

### Age at treatment initiation

According to observational data, rhGH treatment is usually initiated at a mean age of 7 y, as reported by Takeda et al. (91) Increasingly, rhGH treatment is initiated earlier (10, 17, 72). Published data support benefits of rhGH treatment when started between 4–6 mo of age, (25, 34) but some experts are currently treating from as early as 3 mo. There was no consensus reached on age of rhGH start although all agreed to the benefits of treating *before* the onset of obesity, which often begins by 2 y of age.

### Dosing

**a. Infants and children.** Evidence for efficacy in infants and children is based on trials using a dosage of 1.0 mg/m<sup>2</sup>/day achieved within approximately one month of starting treatment (50). Given that patients with PWS exhibit variable degrees of GHD and that salutary outcomes in RCTs were associated with doses of 1.0 mg/m<sup>2</sup>/day (higher than the dose of rhGH routinely used in congenital GHD) or higher, it is unknown whether similar outcomes could be replicated with rhGH doses that result in consistently normal IGF-I levels. IGF-I levels and IGF-I/IGFBP-3 ratios rise to above 2SD in some patients on this dosage, theoretically presenting some risk (83). (26, 35, 38, 40, 51, 92, 93) The efficacy of doses lower than 1.0 mg/m<sup>2</sup>/day administered over a long period of time is unknown, however it has been suggested that the efficacy of lower doses of rhGH on body composition is decreased (50, 51). Infants and children with PWS should start with a daily dose of 0.5 mg/m<sup>2</sup>/day subcutaneously to minimize side effects, with subsequent adjustments toward 1.0 mg/m<sup>2</sup>/day; there was disagreement as to how rapidly this should occur (3–6 mo). If not using body surface area (BSA)-based calculations (recommended) it was felt prudent to base dose calculations on a nonobese weight for height in cases where overweight for height (BMI = 8<sup>5</sup>th to 9<sup>5</sup>th percentile) or obesity exists, particularly when starting rhGH therapy. There was a difference of opinion regarding the timing and frequency of IGF-I measurement before increasing dosage to 1.0 mg/m<sup>2</sup>/day in the pediatric population with PWS. Notably, patients with PWS appear to be highly sensitive to GH in terms of IGF-I generation (94, 94), and standard rhGH doses often results in IGF-I levels outside the normal range. Since lymphoid hyperplasia is related to the levels of IGF-I, (95) this might increase the risk of sleep apnea (81).

**b. Adults.** In adults with PWS rhGH doses tested in placebo-controlled and open-label trials have varied between 0.2 and 1.6 mg per day s.c., depending on the time period under rhGH treatment, weight and induced IGF-I levels. This dose range gives an acceptable side effect profile, (29, 59, 61–64, 96) as well as beneficial effects on body composition, psychological and behavioral problems, Quality of Life (QoL), and heart function and results in IGF-I levels within the range of age matched controls (59, 61, 63, 64, 96, 97). It was unanimously concluded that in adults with PWS, the optimal IGF-I level, i.e., the level where the rhGH treatment will have clear beneficial effects and at the same time the lowest, possible risk of adverse events, will be a value similar to 0 to +2 SDS (SD score, z-score) for age-matched controls.

### Monitoring and Potential Side Effects

There was unanimous agreement that rhGH therapy should be supervised by pediatric or adult endocrinologists, ideally those experienced with the care of patients with PWS. Periodic monitoring of the safety and efficacy of the treatment is mandatory (Table 3).

In the past, rhGH therapy dose adjustments in children were routinely performed based on growth response and/or weight (or BSA) increases. Epidemiological data suggesting a potential link between IGF-I levels and some adverse events (83, 84, 98, 104) have motivated investigators to consider maintaining IGF-I levels within the physiologically normal range (0 to +2 SDS), an approach shown to be feasible in other conditions, such as rhGH treatment of children with idiopathic short stature or small for gestational age (SGA), where pharmacologic doses are used (99, 100). Workshop participants felt that for the pediatric age range, IGF-I levels in patients with PWS on rhGH treatment could therefore safely be maintained within the upper part of normal range (+1 to +2 SDS) for healthy, age-matched normal individuals. For the adult population, where discontinuation of treatment because of side effects is more frequently noted, an IGF-I of 0 to +2 SDS was suggested.

Table 4 summarizes the side effects that should be routinely monitored. While rhGH therapy has a favorable safety profile, the postulated association between unexpected death and rhGH treatment in children with PWS deserves special attention not only in the consenting process and pretreatment evaluation, but also during treatment (16, 97, 101, 102). During rhGH treatment, changes in breathing (particularly during sleep) should be promptly reported and evaluated by repeat oximetry and/or polysomnography within the first 3 to 6 mo of starting therapy. Longer-term rhGH therapy has been associated with improvement in respiratory function in chil-

**Table 3.** Multi-disciplinary Evaluation of Pediatric Patients<sup>a</sup> with PWS During rhGH Treatment<sup>b</sup>

● Regular clinical assessment of height, weight, BMI, pubertal status, scoliosis, IGF-I, and side effects every 3–6 months
● Clinical assessment of body composition every 6–12 months by one or more of the following: waist circumference, skinfold thickness, DEXA (or other available technique for determining body fat and lean body mass).
● Yearly bone age determination, particularly during pubertal age range
● IGF-I determination every 6–12 months
● ENT assessment and sleeping oxymetry, or ideally, repeat polysomnography within the first 3–6 months
● If development or worsening of sleep-disordered breathing, snoring, or enlargement of tonsils and adenoids, ENT assessment, polysomnography, and IGF-I measurement are mandatory
● Fasting glucose, insulin and HbA1c; if obese and/or older than 12 y and/or acanthosis nigricans and/or family history of diabetes/ethnic risk factors, OGTT
● x-ray ± orthopedic assessment if concern or doubt about scoliosis progression
● Monitoring for hypothyroidism yearly or if symptoms
● Lipid profiles and liver function tests and/or liver ultrasound according to family history, age and weight status as per clinical guidelines for non-PWS patients, with referral to gastroenterologist if non-alcoholic fatty liver disease is suspected
● In cases of acute illness and suggestive symptomatology, obtain critical blood samples for measurement of cortisol and ACTH levels if possible, and assess adrenal glucocorticoid response to provocative testing where indicated
Continued contact with nutritionist, physiotherapist/occupational therapist, speech therapist and psychologist (frequency to determine on a case-by-case basis)
● If marked deterioration in behavior with or without overt psychiatric symptoms, psychiatry assessment

<sup>a</sup>Applicable to adult patients with PWS with the exception of the radiologic evaluations (bone age monitoring, scoliosis monitoring).

<sup>b</sup>Adapted and modified from: Goldstone AP, Holland AJ, Hauffa BP, Hokken-Koelega AC, Tauber M. Recommendations for the diagnosis and management of Prader-Willi syndrome. *J Clin Endocrinol Metab.* 2008;93(11):p 4188.(17)

**Table 4.** rhGH Potential Side Effects to Monitor<sup>a</sup>

■ Changes in physical features and body proportions (faces, hands, feet) or bone growth
■ Peripheral edema
■ Joint pain
■ Sleep apnea/disordered breathing: snoring, respiratory pauses, excessive daytime sleepiness
■ Pseudotumor cerebri/ benign intracranial hypertension: headache, visual changes, nausea, dizziness
■ Slipped capital femoral epiphysis: hip and/or knee pain, gait disturbance
■ Insulin resistance: elevated fasting insulin
■ Decreased T4 level (requires measurement of T3 to differentiate from true central hypothyroidism)
■ Scoliosis (recent data suggest no causal relationship or exacerbation of progression)
<u>Long-term Surveillance on, or following, cessation of rhGH</u>
■ Glucose intolerance/Type 2 Diabetes Mellitus particularly in obese patients or patients with positive family history
■ Epilepsy (no known relationship but should be reported)
■ <i>De novo</i> neoplasia (no known relationship but should be reported)
■ Stroke, intracranial bleeding

<sup>a</sup>Shown are the reported side effects of GH treatment primarily in the pediatric population with, or without PWS. No published data are available concerning GH treatment in adults with PWS on joint pain, sleep apnea, epilepsy, intracranial hypertension, neoplasia and stroke/intracranial bleeding. Furthermore, none of the studies in PWS adults (longest follow-up 5 yr) have reported breast tenderness/enlargement, unexpected death.

dren and adults, primarily due to improvements in respiratory muscle function as indicated by increases in peak expiratory flow (35, 50, 96). Data concerning rhGH effects on central respiratory drive are few and are difficult to interpret because of multiple confounders (103, 104). No data are available concerning rhGH treatment and sleep apnea in adults with PWS.

There was a consensus to include an evaluation of diabetes risk (determination of HbA1c, fasting glucose and insulin) in patients with PWS who are obese and/or who are older than 12 y or who have a positive family history of diabetes. Further studies are needed to refine these recommendations since insulin sensitivity and risk of meta-

bolic syndrome in patients with PWS may vary depending upon degree of obesity, adipose tissue distribution, genetic background risk and use of antipsychotics (105–109).

### Tolerability

Tolerability of rhGH by pediatric and adult patients with PWS is high, according to the workshop participants involved in RCTs. (7, 24, 25, 29, 35, 36, 38, 41, 59–64, 96) However, relatively few adults with PWS have been studied and insufficient data are available to judge whether adverse effects of rhGH, death due to other causes, or personal choice accounted for treatment cessation. For children with PWS treated with rhGH and fol-

lowed in phase 4 postmarketing surveys, the reported rate of side effects leading to treatment cessation in trials overall is low (110). The enthusiasm of parents of PWS children for rhGH therapy suggests that early cessation is lower than in other rhGH-treated patients with conditions like idiopathic short stature, Turner syndrome, and children who are born SGA.

### Clinical Outcome Variables and rhGH Non-Responsiveness

In untreated children with PWS, auxological and body composition parameters tend to deteriorate over time, so if these continue to improve or to stabilize, treatment is usually continued until adult height or near-adult height is reached. However, if adult height attainment is used for the decision to stop rhGH therapy in adolescents with PWS, it is important to note that these patients often experience premature adrenarche and obesity, causing early closure of growth plates (111, 112).

For adults with PWS and GHD, treatment duration depends on primary clinical outcome (body composition, lipid metabolism, physical and psycho-social functioning) and occurrence of side effects (impairments of glucose metabolism, edema, heart disease) (62).

Controlled studies of continuous treatment through childhood, adolescence and the transitional period into adulthood are not available in PWS, yet there is a strong likelihood of continued benefit by inference from non-PWS organic GHD and observational studies in PWS.

It was agreed that psychomotor development should be the priority during infancy with body composition and growth becoming important during childhood and adolescence. The data on cognitive benefits of rhGH treatment in the pediatric setting are limited, but should positive effects be extended, this would likely become a top treatment priority (25, 26, 35, 113). The workshop participants concluded that metabolic outcome variables should become the important priority in adults with PWS, although muscular hypotonia, mental retardation and psycho-social dysfunction should continue to receive attention throughout the lifespan. The ultimate goal is an improvement in the patient's well-being.

The definition of nonresponsiveness to rhGH is arbitrary, since there is a continuum in GH response. Many other anthropomorphic and biochemical parameters plateau after some years of treatment, but deteriorate subsequently if rhGH is stopped. Response criteria to rhGH will vary according to age, pubertal status, degree of growth retardation and duration of therapy. Workshop participants felt that a successful first year pediatric response to rhGH treatment includes a delta height SDS > 0.3, a first year height velocity increment of [mteq] 3 cm/year, or a

height velocity SDS [mteq] +1. **Workshop participants acknowledged the difficulty of having alternative, easily measurable, robust, validated, affordable clinical endpoints other than the initial growth response. When possible, attempts should be made to document favorable changes in psychomotor progress and development, body composition, strength and exercise tolerance and QoL for both patient and caregivers, and findings should be reviewed with all involved in the decision to continue treatment.** Parameters that define the sustained success of therapy include adult height SDS, adult height SDS minus height SDS at start of rhGH, adult height minus predicted height at start of treatment, and adult height minus target height (based on sex-corrected mean parental height). Emerging data on genotype-phenotype correlations relevant to specific outcome measures targeted with rhGH therapy need to be repeated in additional cohorts before firm conclusions can be drawn (12, 101, 107).

### Use of Adjunct Therapies

Nutritional management remains the mainstay of treatment of patients with PWS even during rhGH therapy. Regular contact with a dietitian knowledgeable about PWS is essential, initially to calculate desirable caloric increases during the failure to thrive period often observed in infants with PWS. Once the failure to thrive period is over, caloric requirements vary according to the nutritional phase of the patient and are typically approximately 80% those of children and adults without PWS (114). This entails surveillance of vitamin and trace element intake to insure that recommended daily allowances are achieved. When hyperphagia begins, or if weight percentiles are increasing (usually age 2–4 y), close supervision must be maintained to minimize food stealing. Locking the kitchen, refrigerator, and/or cupboards is often necessary. As members of the treating team, dietitians must regularly reinforce adherence to diet, environmental control and programmed physical activity (115–117).

In some children, particularly those who have inadequate dietary, environmental and/or lifestyle interventions, unacceptable weight gain may occur during therapy. All attempts should be made to sensitize the family as to the increased risks for obesity-related health concerns, and to explain that rhGH therapy should not be viewed as a weight loss solution.

Recent studies in adolescent and adult patients with PWS (90% untreated with rhGH) using cyclic, intensive exercise and nutritional restriction successfully lead to BMI reductions during the period of participation in the study (up to 6 y) (118). Long-term, rigorous exercise and strict nutritional control have not been tested against rhGH therapy at any age.



Multiple pharmacological approaches in PWS aimed at increasing energy expenditure and weight loss have not been successful in limited short-term trials, and are summarized in Table 5. The workshop participants agreed that surgical strategies to achieve weight loss have not been

successful long term (initial weight loss followed by weight regain) and have been associated with frequent complications (intestinal malabsorption, infectious complications, gastric perforation and death), and should therefore be discouraged (119–124).

**Table 5.** Adjunct Therapies Attempted in PWS

Pharmacological Strategies	Mechanism of Action	Limitations/Adverse Events	References
Sibutramine	- Noradrenergic reuptake inhibitor  - Induces satiety without reducing metabolic rate	- Modest weight loss efficacy  - Poor long-term compliance	- Padwal <i>et al.</i> , 2007(131)
Orlistat	- Inhibits pancreatic lipase	- Hypertension - Modest weight loss efficacy  - Poor long-term compliance - Gastrointestinal side effects	- Butler <i>et al.</i> , 2006(115)
Bupropion and naltrexone	- Bupropion: Activates central melanocortin pathways in the arcuate nucleus ( $\alpha$ -MSH and $\beta$ -endorphin secretion); decreases hunger and increases energy expenditure - Naltrexone: Opioid inhibitor; blocks $\beta$ -endorphin inhibition of $\alpha$ -MSH release (normal feedback disrupted); decreases hunger and increases energy expenditure	- Ineffective individually, some suggestion that combination therapy may be more effective at weight loss, no published clinical trials in PWS  - Multiple side effects: Nausea, Dry mouth, Headache, Dizziness, Fatigue, Constipation, Insomnia, Possibility of alteration of mood and depression - Contraindicated in acute hepatitis or liver failure	- Greenway <i>et al.</i> , 2009(132)  - Lee and Fujioka, 2009(133)  - Padwal, 2009(134) - Plodkowski <i>et al.</i> , 2009(135) - Zipf and Berntson, 1987(136) - Shapira <i>et al.</i> , 2002(137)
Antiepileptics (Topiramate)	- Anti-seizure drug also used in migraine treatment	- No published clinical trials in PWS	-

(Continued)

Table 5. Continued

Pharmacological Strategies	Mechanism of Action	Limitations/Adverse Events	References
	- Modulatory effects on Na <sup>+</sup> channels, GABAA receptors, and AMPA/kainate	- Multiple side effects: Fatigue, Difficulty concentrating, Paresthesia, Somnolence, Ataxia, Dizziness, Nephrolithiasis, Word-finding difficulty, Mild confusion, Sedation	- Smathers <i>et al.</i> , 2003(138)
Somatostatin analogs	- Affects food-seeking behavior - Inhibits ghrelin secretion	- No benefits on weight or appetite in PWS	- De Waele <i>et al.</i> , 2008(139)
	- Limit the release of insulin	- Decreased insulin secretion	- Haqq <i>et al.</i> , 2003(140)
	- Decreases hyperphagia	- Impaired glucose tolerance	- Haqq <i>et al.</i> , 2003(141)
		- Risk of cholesterol gallstones	- Tan <i>et al.</i> , 2004(142)
			- Tzotzas <i>et al.</i> , 2008(143)
Rimonobant	- Block endocannabinoid receptor CB1 in central and peripheral nervous systems and other key cells involved in body energy metabolism	- Efficacious weight loss	- Motaghedi <i>et al.</i> , 2010(15)
		- Lack of compliance in adults with PWS due to high risk of psychiatric side effects (mood disorders, suicide)	
Anorexigens gut hormones (e.g. exenatide)	- Incretin mimetic: GLP-1 receptor agonist - Increases insulin secretion	- Lack of efficacy in subjects with PWS	- Purtell <i>et al.</i> , 2011(144) - Sze <i>et al.</i> , 2011(145)

(Continued)

Additional studies are required to ascertain the safety, efficacy, and tolerability of alternative pharmacological

**Table 5.** Continued

Pharmacological Strategies	Mechanism of Action	Limitations/Adverse Events	References
CoQ10	- Involved in the production of adenosine triphosphate in the mitochondria	- No observed weight loss effects in PWS  - Possible benefits on psychomotor development, but masked by the natural development	- Eiholzer <i>et al.</i> , 2008(146)
Restrictive bariatric surgery (gastric banding or bypass)	- Several surgical procedures	- Contradictory efficacy results	- Buchwald, 2005(147)
	- Induces weight loss by altering the digestive tract so that nutrients and fats are not absorbed by the body (stomach reduction and/or bypass)	- Limited weight reduction long term	- Antal and Levin, 1996(148)
		- Numerous postoperative issues	- Marinari <i>et al.</i> , 2001(149)
		- Weight regain 1 to 5 y after surgery	- Papavramidis <i>et al.</i> , 2006(150)
	- Frequent complications from the resulting intestinal malabsorption (i.e. nutritional deficiencies)	- Marceau <i>et al.</i> , 2010(151)	
	- Postoperative respiratory and infectious complications	- Scheimann <i>et al.</i> , 2008(152)	
	- Gastric perforation		
	- Death		

approaches to weight loss in PWS either alone or in combination with rhGH. Thus there is insufficient evidence to support use of currently available obesity management medications or bariatric surgery in conjunction with rhGH treatment for weight reduction in patients with PWS, and indeed, some may be contraindicated.

### Issues of Consent/Assent

There are differences in national legal regulations dictating when a child reaches the age of consent (e.g, 18 in many countries). Informed assent of a child is required in circumstances where he or she is beginning to make more complex decisions; this requires that the child is capable of

some degree of understanding and appreciation of the clinical reasoning.

Even in cases of cognitive disability in an older child or adolescent with PWS, it is optimal that legal guardians remain surrogate decision-makers, but that physicians strive to obtain the patient's assent for rhGH therapy, even if the patient has limited decision-making capacity. An adult patient with intellectual disability due to PWS may be capable of consenting to rhGH treatment if he/she is able to understand and appreciate his or her clinical circumstances. In circumstances in which an adult patient does not have the capacity to consent, a surrogate decision-maker is appropriate, guided by country- and state-specific guardianship laws (125). This assent/consent process fosters a doctor – patient relationship based on partnership, mutual trust, understanding and respect (32, 126, 127).

It is not known to what degree the cognitive impairment of the individual with PWS plays a role in physicians' lack of recommendation for rhGH use, whether because of perceived difficulty in obtaining truly informed consent or because of physicians' views on healthcare priorities. All participants felt that cognitive impairment should not be a barrier or a contraindication to discussion of rhGH treatment with the patient and caregivers.

### Issues of Fair Access to rhGH.

According to several PWS support associations, access to the option of rhGH therapy is currently unevenly provided even in countries with drug approval for this indication. Members of the workshop felt that several factors currently contribute to differences in the availability of the option for rhGH therapy for patients with PWS: 1) A lack of parental awareness of treatment options and general impediments to healthcare, 2) Inadequate numbers of physician willing and qualified to prescribe rhGH and to regularly assess treatment response and potential adverse events, 3) Inability to pay for rhGH either through personal wealth or by participation in a healthcare system that supports rhGH treatment and monitoring costs for PWS.

In considering efficiency and best distribution of healthcare resources among desirable interventions for patients with PWS, a long list of important interventions must be considered, such as occupational and physical therapy (PT), speech and language therapy, social skills therapy, weight management therapy and behavioral therapy, ophthalmologic and orthopedic interventions, and neurologic, psychiatric and endocrine care (replacement therapies for sex hormones, GH, L-thyroxin, cortisol). Although rhGH therapy is costly, (91) compared to the cost of the provision of all of these services, the cost of rhGH

may be relatively modest. However, a true understanding of the healthcare burden of treating individuals with PWS requires long term health outcome research studies.

### Future Directions

At the end of the meeting, workshop participants were asked to individually rank, in order of importance, areas needing further research that had been discussed during breakout sessions. It is not surprising that continued surveillance of long-term effects of rhGH treatment was considered the top priority, particularly with regards to glucose metabolism and diabetes risk, as well as sleep and sleep-disordered breathing. The impact of rhGH treatment on quality of life (QOL), not only of patients but also of their families, was also ranked as an important aspect of treatment response that needs additional documentation. Most of the attendees who were not physicians saw an important place for future clinical trials combining rhGH with other therapeutic approaches, particularly those targeting hyperphagia and behavior. The top 10 areas that received the highest priority scores can be seen in Table 6.

### Conclusion

It is hoped that this PWS Workshop Summary will give patients, caregivers and physicians a framework with which to optimize care. More importantly, it is hoped that it will help harmonize the healthcare access of the pediatric and adult populations with PWS, not just with regards to rhGH treatment but also with regards to the need for life-long follow-up of these patients by multidisciplinary teams with experience in PWS. Finally, we stress the importance of the ethical framework in which healthcare specialists working with patients with PWS should practice, and which should emphasize principles of informed consent/assent, respect for persons and distributive justice.

### Acknowledgments

The workshop participants would like to thank the Foundation for Prader-Willi Research and the EVIDEM Collaboration, in particular, Dr. Mireille Goetghebeur (President of the nonprofit EVIDEM Collaboration), for her help in preparing the methodological approach to this CPG and, along with Patricia Campbell, for the design and support of the PWS GH Evidence Registry and Workshop Website. We would also like to thank Dominika Kozubaska, CHU-Ste-Justine Research Center, for her expert administrative assistance of the workshop. We gratefully acknowledge the provision of rhGH safety data from the following com-

**Table 6.** Areas Regarding rhGH Use for PWS Requiring Prioritized Attention in Future Studies<sup>a</sup>**TOP 10 areas for further research**

- i. Effects of rhGH therapy in adults with PWS on quality of life
- ii. Long-term post-treatment effect of rhGH on mortality and morbidity using registries
- iii. The optimal timing and dosage of rhGH treatment initiation in early life
- iv. The effect of rhGH interruption at completion of growth
- v. Effects of rhGH on behavior and cognitive function across the age range
- vi. Impact of rhGH treatment on activities of daily living and well-being as defined by WHO
- vii. Influence of IGF-I titration on clinical effects
- viii. Effect of rhGH on glucose metabolism/diabetes risk, mainly long term effect
- ix. Effects of rhGH therapy on sleep and sleep-disordered breathing in PWS adults
- x. RCT trials investigating combination approaches to treatment

*Additional areas for future research*

- xi. Effects of GH/IGF-I on nasopharyngeal tissue and mainly if adenotonsillectomy changes the course or may avoid potential side effects of rhGH on sleep disorders and OSA
- xii. Dose response relationships investigating efficacy of physiologic (rather than pharmacologic) dosing
- xiii. Effects of rhGH treatment in children and adults on visceral adiposity and ectopic fat e.g. muscle, liver and pancreas
- xiv. Effects of rhGH on timing of development or severity of hyperphagia
- xv. Effect of rhGH on bone maturation and premature pubarche
- xvi. Effects on structural brain development
- xvii. Scoliosis and slipped capital femoral epiphysis in children
- xviii. Is there hypersensitivity to rhGH in PWS?
- xix. Thyroid function before and after rhGH
- xx. Effects on cardiac function
- xxi. Effects of rhGH on lipid metabolism
- xxii. Effects of rhGH on water retention
- xxiii. Intracranial hypertension (difficult to assess in young children)

<sup>a</sup>All participants were asked to discuss areas for future investigation within breakout groups. All participants were then asked to order, by priority, using a secret ballot.

panies: Genetech-Hoffman LaRoche, Lilly, Novo-Nordisk, Pfizer, and Serono.

Address all correspondence and requests for reprints to: Corresponding author, to whom reprint requests should be directed: Cheri Deal, Ph.D., M.D., F.R.C.P.C., Endocrine Service, CHU-Sainte-Justine/Université de Montréal, 3175 Côte Ste-Catherine, Montréal, Québec H3T 1C5, CANADA, Cheri.L.Deal@umontreal.ca.

<sup>a</sup> Participants of the workshop: Ambler, Geoffrey R.: Institute of Endocrinology and Diabetes, The Sydney Children's Hospitals Network (Westmead) and The University of Sydney, Australia, Battista, Renaldo: Department of Health Administration, University of Montreal, Canada, Beauloye, Veronique: Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, France, Berall, Glen: Division of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, The Hospital for Sick Children, Canada, Biller, Beverly MK: Department of Medicine, MA General Hospital, USA, Butler, Merlin G: Departments of Psychiatry, Behavioral Sciences and Pediatrics, KS University Medical Center, USA, Cassidy, Suzanne B.: Division of Medical Genetics, Department of Pediatrics, University of California, USA, Chihara, Kazuo: Hyogo Prefectural Kakogawa Medical Center, Japan, Cohen, Pinchas: Department of Pediatric Endocrinology, Mattel Children's Hospital at UCLA, USA, Craig, Maria: Institute of Endocrinology and Diabetes, Sydney Children's Hospital Network (Westmead); University of New South Wales, University of Sydney, Australia, Farholt, Stense: Centre for Rare Diseases, Aarhus University Hospital Skejby, Denmark, Goetghebeur, Mireille: LA-SER, Montreal Canada; Department of Health Administration, University of Montreal, Canada; EVIDEM Collaboration, Canada, Goldstone, Anthony

P.: Metabolic and Molecular Imaging Group, MRC Clinical Sciences Centre, Imperial College London, and Imperial Centre for Endocrinology, Hammersmith Hospital, UK, Gregg, Tiziana: Spine and Surgical Division, Istituto Ortopedico Rizzoli, Italy, Grugni, Graziano: Pediatric Endocrinologist, Istituto Auxologico Italiano, Research Institute, Italy, Hokken-Koelega Anita C.: Erasmus University Medical Center/ Sophia Children's Hospital Rotterdam, Johannsson, Gudmundur: Department of Endocrinology, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Johnson, Keegan: Foundation for Prader-Willi Research, USA, Kemper, Alex: Department of Pediatrics, Duke University, USA, Kopchick, John J.: Edison Biotechnology Institute, OH University, USA, Malozowski, Saul: National Institutes of Health, USA, Miller, Jennifer: Pediatric Endocrinologist, University of Florida, USA, Mogul, Harriette R.: Division of Endocrinology, NY Medical College, USA, Muscatelli, Françoise: Mediterranean Institute of Neurobiology (INMED), INSERM U901, France, Nergardh, Ricard: Division of Pediatric Endocrinology, Astrid Lindgren Childrens Hospital, Karoliska Institute, Sweden, Nicholls, Robert D.: Division of Medical Genetics, Department of Pediatrics, Children's Hospital of Pittsburgh, USA, Radovick, Sally: Pediatric Endocrinology, John Hopkins Children's Center, USA, Rosenthal, M. Sara: Associate Professor, Program for Bioethics, Depts. of Internal Medicine and Pediatrics, University of Kentucky, USA, Sipilä, Ilkka: Pediatrics, Hospital for Children and Adolescents, University of Helsinki, Finland, Tarride, Jean-Eric: Associate professor (part Time), Department of Clinical Epidemiology and Biostatistics, McMaster University, Canada, Tony, Michèle: Département d'administration de la santé, Université de Montréal, Canada, Vogels, Annick: Kinder-en jeugdpsychiater, Centrum Menselijke Erfelijkheid, Belgium, Waters, Michael J.: Institute for Mo-

lecular Bioscience and School of Biomedical Sciences, University of Queensland, Australia

**Disclosure Statement:** DBA, RB, RDN, MGB, VB, SBC, KC, MC, JSC, AK, GG, MG, TG, JJK, JM, SM, RN, SR, MT, AV, and MJW have nothing to declare. GRA has previously consulted for Pfizer (March 2012 to June 2012) and received grant support from Pfizer (2011 and 2012) and Ipsen (2011 and 2012). GB has previously consulted for Nestle Nutrition, has served as an expert witness for various legal cases, has received lecture fees from Abbott Nutrition, is an inventor on Hong Kong patent 07111326.5, Europe patent 05759244.6, Australia patent 2005253661, USA patent 11/570,740, Singapore patent 200608776-1, Japan patent 2007-515753, China patent 20058002768.1, and USA patent 12/401,505, and consults for Abbott Nutrition. BMKB received grant support from Novo Nordisk (2011 and 2012), Pfizer (until Dec 2011), and Serono (2011), and consults for Novo Nordisk and Pfizer. PC has previously consulted for Ipsen (2011), Medivation (2011), Therat-technologies (2011), L-Nutra (2011), and Serono (2011), has equity interests in CohBar Inc., received grant support from Amgen, Genentech, Eli Lilly and Pfizer, is an inventor on USA Patent 02307K-182710, and consults for Novo Nordisk and Teva. CD has consulted and received lecture fees for Lilly, Serono, Sandoz, Novo Nordisk and Pfizer. SF has received lecture fees from NovoNordisk. CH received lecture fees from Pfizer, Novo Nordisk and IPSEN. APG has received a grant from Pfizer 2011–2012. ACHK received lecture fees from Novo Nordisk, Pfizer, and Ferring, has received unrestricted research grants from Pfizer Netherlands for the Dutch PWS Cohort study 2010–2012 and the Dutch SGA study 2010–2012, and an unrestricted research grant from Novo Nordisk for the Dutch IUGR and Follow-up studies 2010–2012. GJ has received lecture fees from NovoNordisk, Pfizer, Eli Lilly, Otsuka, and Merck Serono, and consults for Viropharma, Otsuka and Astra Zeneca. KJ was previously employed by Ethecca and Cryptologie (2000–2005) and consults for Foundation for Prader Willi Research. HRM has received grant support from Glaxo Smith Kline (2007–2012), Lilly (2003–2012) and consults for Pfizer. FM is an inventor on FRANCE patent EP10305545.5. SR has previously consulted for Genentech on a Grant advisory committee and has received grant support from NIH. IS has received lecture fees and consults for Oy Eli Lilly Finland Ab, NovoNordisk Farma Oy, and Pfizer Oy. JET is employed by AstraZeneca Canada since May 28 2012. MT received lecture fees from Pfizer and Novo Nordisk and is on a Pfizer and Ipsen advisory board.

<sup>1</sup>National Cooperative Growth Study (Genentech), Genetics and Neurendocrinology of Growth International Study (Lilly), Kabi International Growth Study (Pfizer), GH Monitor (EMD Serono), Nordinet and ANSWER (Novo Nordisk).

This work was supported by This workshop was supported by grants from the Growth Hormone Research Society and from the Foundation for Prader-Willi Research. A grant-in-kind was provided by the EVIDEM Collaboration for support of the PWS Workshop Website and for subsequently maintaining the site open to the public. Michèle Tony is supported by a doctoral scholarship from APOGÉE-Net/CanGèneTest Network.

## References

- Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader-Willi syndrome. *Genet Med*. 2012;14(1):10–26.
- Butler MG. Prader-Willi Syndrome: Obesity due to Genomic Imprinting. *Curr Genomics*. 2011;12(3):204–215.
- Whittington JE, Butler JV, Holland AJ. Changing rates of genetic subtypes of Prader-Willi syndrome in the UK. *Eur J Hum Genet*. 2007;15(1):127–130.
- Eiholzer U, Stutz K, Weinmann C, Torresani T, Molinari L, Prader A. Low insulin, IGF-I and IGFBP-3 levels in children with Prader-Labhart-Willi syndrome. *Eur J Pediatr*. 1998;157(11):890–893.
- Tauber M, Barbeau C, Jouret B, Pienkowski C, Malzac P, Moncla A, Rochiccioli P. Auxological and endocrine evolution of 28 children with Prader-Willi syndrome: effect of GH therapy in 14 children. *Horm Res*. 2000;53(6):279–287.
- Corrias A, Bellone J, Beccaria L, Bosio L, Trifiro G, Livieri C, Ragusa L, Salvatoni A, Andreo M, Ciampalini P, Tonini G, Crino A. GH/IGF-I axis in Prader-Willi syndrome: evaluation of IGF-I levels and of the somatotroph responsiveness to various provocative stimuli. Genetic Obesity Study Group of Italian Society of Pediatric Endocrinology and Diabetology. *J Endocrinol Invest*. 2000;23(2):84–89.
- Hoybye C, Frystyk J, Thoren M. The growth hormone-insulin-like growth factor axis in adult patients with Prader Willi syndrome. *Growth Horm IGF Res*. 2003;13(5):269–274.
- Grugni G, Crino A, Pagani S, Meazza C, Buzi F, De Toni T, Gargantini L, Pilotta A, Pozzan GB, Radetti G, Ragusa L, Salvatoni A, Sartorio A, Bozzola M. Growth hormone secretory pattern in non-obese children and adolescents with Prader-Willi syndrome. *J Pediatr Endocrinol Metab*. 2011;24(7–8):477–481.
- Bekx MT, Carrel AL, Shriver TC, Li Z, Allen DB. Decreased energy expenditure is caused by abnormal body composition in infants with Prader-Willi Syndrome. *J Pediatr*. 2003;143(3):372–376.
- Diene G, Mimoun E, Feigerlova E, Caula S, Molinas C, Grandjean H, Tauber M. Endocrine disorders in children with Prader-Willi syndrome—data from 142 children of the French database. *Horm Res Paediatr*. 2010;74(2):121–128.
- Grugni G, Crino A, Bertocco P, Marzullo P. Body fat excess and stimulated growth hormone levels in adult patients with Prader-Willi syndrome. *Am J Med Genet A*. 2009;149A(4):726–731.
- Grugni G, Giardino D, Crino A, Malvestiti F, Ballarati L, Di Giorgio G, Marzullo P. Growth hormone secretion among adult patients with Prader-Willi syndrome due to different genetic subtypes. *J Endocrinol Invest*. 2011;34(7):493–497.
- van Nieuwpoort IC, Sinnema M, Castelijns JA, Twisk JW, Curfs LM, Drent ML. The GH/IGF-I axis and pituitary function and size in adults with Prader-Willi syndrome. *Horm Res Paediatr*. 2011;75(6):403–411.
- Lee PD, Wilson DM, Rountree L, Hintz RL, Rosenfeld RG. Linear growth response to exogenous growth hormone in Prader-Willi syndrome. *Am J Med Genet*. 1987;28(4):865–871.
- Burman P, Ritzen EM, Lindgren AC. Endocrine dysfunction in Prader-Willi syndrome: a review with special reference to GH. *Endocr Rev*. 2001;22(6):787–799.
- Tauber M, Diene G, Molinas C, Hebert M. Review of 64 cases of death in children with Prader-Willi syndrome (PWS). *Am J Med Genet A*. 2008;146(7):881–887.
- Goldstone AP, Holland AJ, Hauffa BP, Hokken-Koelega AC, Tauber M. Recommendations for the diagnosis and management of Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2008;93(11):4183–4197.
- McCandless SE. The Committee on Genetics. Clinical report: health supervision for children with Prader-Willi Syndrome. *Pediatrics*. 2011;127(1):195–204.
- Craig ME, Johnson AM, Cowell CT. Recombinant growth hormone in Prader-Willi syndrome (protocol). *The Cochrane Library*. 2009;(4):1–7.
- de Lind van Wijngaarden RF, Festen DA, Otten BJ, van Mil EG, Rotteveel J, Odink RJ, vanLeeuwen M, Haring DA, Bocca G, Mieke Houdijk EC, Hokken-Koelega AC. Bone mineral density and effects of growth hormone treatment in prepubertal children with Prader-

- Willi syndrome: a randomized controlled trial. *J Clin Endocrinol Metab.* 2009;94(10):3763–3771.
21. de Lind van Wijngaarden RF, de Klerk LW, Festen DA, Duivenvoorden HJ, Otten BJ, Hokken-Koelega AC. Randomized controlled trial to investigate the effects of growth hormone treatment on scoliosis in children with Prader-Willi syndrome. *J Clin Endocrinol Metab.* 2009;94(4):1274–1280.
  22. de Lind van Wijngaarden RF, Cianflone K, Gao Y, Leunissen RW, Hokken-Koelega AC. Cardiovascular and metabolic risk profile and acylation-stimulating protein levels in children with Prader-Willi syndrome and effects of growth hormone treatment. *J Clin Endocrinol Metab.* 2010;95(4):1758–1766.
  23. Festen DA, van Toorenbergen A, Duivenvoorden HJ, Hokken-Koelega AC. Adiponectin levels in prepubertal children with Prader-Willi syndrome before and during growth hormone therapy. *J Clin Endocrinol Metab.* 2007;92(4):1549–1554.
  24. Festen DA, de Lind vW, van Eekelen M, Otten BJ, Wit JM, Duivenvoorden HJ, Hokken-Koelega AC. Randomized controlled GH trial: effects on anthropometry, body composition and body proportions in a large group of children with Prader-Willi syndrome. *Clin Endocrinol (Oxf).* 2008;69(3):443–451.
  25. Festen DA, Wevers M, Lindgren AC, Bohm B, Otten BJ, Wit JM, Duivenvoorden HJ, Hokken-Koelega AC. Mental and motor development before and during growth hormone treatment in infants and toddlers with Prader-Willi syndrome. *Clin Endocrinol (Oxf).* 2008;68(6):919–925.
  26. Myers SE, Whitman BY, Carrel AL, Moerchen V, Bekx MT, Allen DB. Two years of growth hormone therapy in young children with Prader-Willi syndrome: physical and neurodevelopmental benefits. *Am J Med Genet A.* 2007;143(5):443–448.
  27. Reus L, Zwarts M, van Vlimmeren LA, Willemsen MA, Otten BJ, Nijhuis-van der Sanden MW. Motor problems in Prader-Willi syndrome: A systematic review on body composition and neuromuscular functioning. *Neurosci Biobehav Rev.* 2011;35(3):956–969.
  28. Sanchez-Ortiga R, Klibanski A, Tritos NA. Effects of Recombinant Human Growth Hormone Therapy in Adults with Prader-Willi Syndrome: A Meta-Analysis. *Clin Endocrinol (Oxf).* 2011;77(1):86–93.
  29. Sode-Carlson R, Farholt S, Rabben KF, Bollerslev J, Schreiner T, Jurik AG, Christiansen JS, Hoybye C. One year of growth hormone treatment in adults with Prader-Willi syndrome improves body composition: results from a randomized, placebo-controlled study. *J Clin Endocrinol Metab.* 2010;95(11):4943–4950.
  30. Goetghebeur MM, Wagner M, Khoury H, Levitt RJ, Erickson LJ, Rindress D. Evidence and Value: Impact on DEcisionMaking - the EVIDEM framework and potential applications. *BMC Health Serv Res.* 2008;8(1):270.
  31. Goetghebeur MM, Wagner M, Khoury H, Rindress D, Gregoire JP, Deal C. Combining multicriteria decision analysis, ethics and health technology assessment: applying the EVIDEM decisionmaking framework to growth hormone for Turner syndrome patients. *Cost Eff Resour Alloc.* 2010;8(1):4.
  32. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: Ethical principles and Guidelines for the Protection of Human Subjects of Research. Washington, Department of Health, Education, and Welfare, 18 avril 1979 [updated 1979 Apr 18; cited 2011 Oct. 5]; Available from: URL:<http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>
  33. Carrel AL, Myers SE, Whitman BY, Allen DB. Growth hormone improves body composition, fat utilization, physical strength and agility, and growth in Prader-Willi syndrome: A controlled study. *J Pediatr.* 1999;134(2):215–221.
  34. Carrel AL, Moerchen V, Myers SE, Bekx MT, Whitman BY, Allen DB. Growth hormone improves mobility and body composition in infants and toddlers with Prader-Willi syndrome. *J Pediatr.* 2004;145(6):744–749.
  35. Haqq AM, Stadler DD, Jackson RH, Rosenfeld RG, Purnell JQ, LaFranchi SH. Effects of growth hormone on pulmonary function, sleep quality, behavior, cognition, growth velocity, body composition, and resting energy expenditure in Prader-Willi syndrome. *J Clin Endocrinol Metab.* 2003;88(5):2206–2212.
  36. Hauffa BP. One-year results of growth hormone treatment of short stature in Prader-Willi syndrome. *Acta Paediatr Suppl.* 1997;423:63–65.
  37. Lindgren AC, Hagenas L, Muller J, Blichfeldt S, Rosenborg M, Brismar T, Ritzen EM. Effects of growth hormone treatment on growth and body composition in Prader-Willi syndrome: a preliminary report. *The Swedish National Growth Hormone Advisory Group. Acta Paediatr Suppl.* 1997;423:60–62.
  38. Lindgren AC, Hagenas L, Muller J, Blichfeldt S, Rosenborg M, Brismar T, Ritzen EM. Growth hormone treatment of children with Prader-Willi syndrome affects linear growth and body composition favourably. *Acta Paediatr.* 1998;87(1):28–31.
  39. Myers SE, Carrel AL, Whitman BY, Allen DB. Physical effects of growth hormone treatment in children with Prader-Willi syndrome. *Acta Paediatr Suppl.* 1999;88(433):112–114.
  40. Myers SE, Carrel AL, Whitman BY, Allen DB. Sustained benefit after 2 years of growth hormone on body composition, fat utilization, physical strength and agility, and growth in Prader-Willi syndrome. *J Pediatr.* 2000;137(1):42–49.
  41. Whitman B, Carrel A, Bekx T, Weber C, Allen D, Myers S. Growth hormone improves body composition and motor development in infants with Prader-Willi syndrome after six months. *J Pediatr Endocrinol Metab.* 2004;17(4):591–600.
  42. Angulo MA, Castro-Magana M, Lamerson M, Arguello R, Accacha S, Khan A. Final adult height in children with Prader-Willi syndrome with and without human growth hormone treatment. *Am J Med Genet A.* 2007;143A(13):1456–1461.
  43. Carrel AL, Myers SE, Whitman BY, Eickhoff J, Allen DB. Long-term growth hormone therapy changes the natural history of body composition and motor function in children with prader-willi syndrome. *J Clin Endocrinol Metab.* 2010;95(3):1131–1136.
  44. Eiholzer U, L'Allemand D, Schlumpf M, Rousson V, Gasser T, Fusch C. Growth hormone and body composition in children younger than 2 years with Prader-Willi syndrome. *J Pediatr.* 2004;144(6):753–758.
  45. Eiholzer U, Meinhardt U, Rousson V, Petrovic N, Schlumpf M, L'Allemand D. Developmental profiles in young children with Prader-Labhart-Willi syndrome: effects of weight and therapy with growth hormone or coenzyme Q10. *Am J Med Genet A.* 2008;146(7):873–880.
  46. Fillion M, Deal C, Van Vliet G. Retrospective study of the potential benefits and adverse events during growth hormone treatment in children with Prader-Willi syndrome. *J Pediatr.* 2009;154(2):230–233.
  47. Galassetti P, Saetrum OO, Cassidy SB, Pontello A. Nutrient intake and body composition variables in Prader-Willi syndrome—effect of growth hormone supplementation and genetic subtype. *J Pediatr Endocrinol Metab.* 2007;20(4):491–500.
  48. Nyunt O, Harris M, Hughes I, Huynh T, Davies PS, Cotterill AM. Benefit of early commencement of growth hormone therapy in children with Prader-Willi syndrome. *J Pediatr Endocrinol Metab.* 2009;22(12):1151–1158.
  49. Carrel AL, Myers SE, Whitman BY, Allen DB. Sustained benefits of growth hormone on body composition, fat utilization, physical strength and agility, and growth in Prader-Willi syndrome are dose-dependent. *J Pediatr Endocrinol Metab.* 2001;14(8):1097–1105.
  50. Carrel AL, Myers SE, Whitman BY, Allen DB. Benefits of long-term GH therapy in Prader-Willi syndrome: a 4-year study. *J Clin Endocrinol Metab.* 2002;87(4):1581–1585.
  51. de Lind van Wijngaarden RF, Siemensa EP, Festen DA, Otten BJ, van Mil EG, Rotteveel J, Odink RJ, Bindels-de Heus GC, van Leeuwen M, Haring DA, Bocca G, Houdijk EC, Hoorweg-Nijman JJ, Vreuls RC, Jira PE, van Trotsenburg AS, Bakker B, Schroor EJ, Pilon JW, Wit JM, Drop SL, Hokken-Koelega AC. Efficacy and safety of

- long-term continuous growth hormone treatment in children with Prader-Willi syndrome. *J Clin Endocrinol Metab.* 2009;94(11):4205–4215.
52. Eiholzer U, L'Allemand D, van dS, I, Steinert H, Gasser T, Ellis K. Body composition abnormalities in children with Prader-Willi syndrome and long-term effects of growth hormone therapy. *Horm Res.* 2000;53(4):200–206.
  53. Eiholzer U, L'Allemand D. Growth hormone normalises height, prediction of final height and hand length in children with Prader-Willi syndrome after 4 years of therapy. *Horm Res.* 2000;53(4):185–192.
  54. Eiholzer U, Meinhardt U, Gallo C, Schlumpf M, Rousson V, L'Allemand D. Association between foot growth and musculoskeletal loading in children with Prader-Willi syndrome before and during growth hormone treatment. *J Pediatr.* 2009;154(2):225–229.
  55. Lindgren AC, Ritzen EM. Five years of growth hormone treatment in children with Prader-Willi syndrome. Swedish National Growth Hormone Advisory Group. *Acta Paediatr Suppl.* 1999;88(433):109–111.
  56. Lindgren AC, Lindberg A. Growth hormone treatment completely normalizes adult height and improves body composition in Prader-Willi syndrome: experience from KIGS (Pfizer International Growth Database). *Horm Res.* 2008;70(3):182–187.
  57. Obata K, Sakazume S, Yoshino A, Murakami N, Sakuta R. Effects of 5 years growth hormone treatment in patients with Prader-Willi syndrome. *J Pediatr Endocrinol Metab.* 2003;16(2):155–162.
  58. Sipila I, Sintonen H, Hietanen H, Apajasalo M, Alanne S, Viita AM, Leinonen E. Long-Term Effects of Growth Hormone Therapy on Patients with Prader-Willi Syndrome. *Acta Paediatr.* 2010;99(11):1712–1718.
  59. Hoybye C, Hilding A, Jacobsson H, Thoren M. Growth hormone treatment improves body composition in adults with Prader-Willi syndrome. *Clin Endocrinol (Oxf).* 2003;58(5):653–661.
  60. Hoybye C, Thoren M, Bohm B. Cognitive, emotional, physical and social effects of growth hormone treatment in adults with Prader-Willi syndrome. *J Intellect Disabil Res.* 2005;49(Pt 4):245–252.
  61. Bertella L, Mori I, Grugni G, Pignatti R, Ceriani F, Molinari E, Ceccarelli A, Sartorio A, Vettor R, Semenza C. Quality of life and psychological well-being in GH-treated, adult PWS patients: a longitudinal study. *J Intellect Disabil Res.* 2007;51(Pt 4):302–311.
  62. Hoybye C. Five-years growth hormone (GH) treatment in adults with Prader-Willi syndrome. *Acta Paediatr.* 2007;96(3):410–413.
  63. Marzullo P, Marcassa C, Campini R, Eleuteri E, Minocci A, Sartorio A, Vettor R, Luizzi A, Grugni G. Conditional cardiovascular response to growth hormone therapy in adult patients with Prader-Willi syndrome. *J Clin Endocrinol Metab.* 2007;92(4):1364–1371.
  64. Mogul HR, Lee PD, Whitman BY, Zipf WB, Frey M, Myers S, Cahan M, Pinyerd B, Southren AL. 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 United States multicenter trial. *J Clin Endocrinol Metab.* 2008;93(4):1238–1245.
  65. EVIDEM Collaboration. Knowledge to action: Growth hormone for Patients with Prader Willi syndrome. Workshop website and multicriteria registry of evidence and quality assessments. EVIDEM Collaboration [updated 2011; cited 2012 Sept 14]; Available from: URL:<http://bit.ly/PWGHIN>
  66. Centre for Evidence Based Medicine. CEBM levels of evidence version #2. Centre for Evidence Based Medicine [updated 2010 Jun 10; cited 2010 Aug. 31]; Available from: URL:<http://www.cebm.net/index.aspx?o=5653>.
  67. EVIDEM Collaboration. Open access prototypes of the Collaborative registry. EVIDEM Collaboration [updated 2010; cited 2010 June 29]; Available from: URL:<http://www.evidem.org/evidem-collaborative.php>
  68. Tony M, Hoybye C, Allen DB, Tauber M, Christiansen JS, Deal C. Use of recombinant human growth hormone therapy in Prader Willi Syndrome Review and Clinical Guidelines. Manuscript in preparation - to be submitted to Growth Hormone and IGF Research Journal 2012.
  69. Angulo M, Castro-Magana M, Mazur B, Canas JA, Vitollo PM, Sarrantonio M. Growth hormone secretion and effects of growth hormone therapy on growth velocity and weight gain in children with Prader-Willi syndrome. *J Pediatr Endocrinol Metab.* 1996;9(3):393–400.
  70. Costeff H, Holm VA, Ruvalcaba R, Shaver J. Growth hormone secretion in Prader-Willi syndrome. *Acta Paediatr Scand.* 1990;79(11):1059–1062.
  71. Davies PS, Evans S, Broomhead S, Clough H, Day JM, Laidlaw A, Barnes ND. Effect of growth hormone on height, weight, and body composition in Prader-Willi syndrome. *Arch Dis Child.* 1998;78(5):474–476.
  72. Tauber M, Cutfield W. KIGS highlights: growth hormone treatment in Prader-Willi Syndrome. *Horm Res.* 2007;68 Suppl 5:48–50.
  73. Thacker MJ, Hainline B, Dennis-Feezle L, Johnson NB, Pescovitz OH. Growth failure in Prader-Willi syndrome is secondary to growth hormone deficiency. *Horm Res.* 1998;49(5):216–220.
  74. Sinnema M, Boer H, Collin P, Maaskant MA, van Roozendaal KE, Schrandt-Stumpel CT, Curfs LM. Psychiatric illness in a cohort of adults with Prader-Willi syndrome. *Res Dev Disabil.* 2011;32(5):1729–1735.
  75. Menendez AA. Abnormal ventilatory responses in patients with Prader-Willi syndrome. *Eur J Pediatr.* 1999;158(11):941–942.
  76. Schluter B, Buschatz D, Trowitzsch E, Aksu F, Andler W. Respiratory control in children with Prader-Willi syndrome. *Eur J Pediatr.* 1997;156(1):65–68.
  77. Williams K, Scheimann A, Sutton V, Hayslett E, Glaze DG. Sleepiness and sleep disordered breathing in Prader-Willi syndrome: relationship to genotype, growth hormone therapy, and body composition. *J Clin Sleep Med.* 2008;4(2):111–118.
  78. Bakker B, Maneatis T, Lippe B. Sudden death in Prader-Willi syndrome: brief review of five additional cases. Concerning the article by U. Eiholzer et al. Deaths in children with Prader-Willi syndrome. A contribution to the debate about the safety of growth hormone treatment in children with PWS (Horm Res 2005;63:33–39). *Horm Res.* 2007;67(4):203–204.
  79. Eiholzer U, Nordmann Y, L'Allemand D. Fatal outcome of sleep apnoea in PWS during the initial phase of growth hormone treatment. A case report. *Horm Res.* 2002;58 Suppl 3:24–26.
  80. Grugni G, Livieri C, Corrias A, Sartorio A, Crino A. Death during GH therapy in children with Prader-Willi syndrome: description of two new cases. *J Endocrinol Invest.* 2005;28(6):554–557.
  81. Miller J, Silverstein J, Shuster J, Driscoll DJ, Wagner M. Short-term effects of growth hormone on sleep abnormalities in Prader-Willi syndrome. *J Clin Endocrinol Metab.* 2006;91(2):413–417.
  82. Riedl S, Blumel P, Zwiauer K, Frisch H. Death in two female Prader-Willi syndrome patients during the early phase of growth hormone treatment. *Acta Paediatr.* 2005;94(7):974–977.
  83. Clayton PE, Banerjee I, Murray PG, Renehan AG. Growth hormone, the insulin-like growth factor axis, insulin and cancer risk. *Nat Rev Endocrinol.* 2011;7(1):11–24.
  84. Carel JC, Ecosse E, Landier F, Meguellati-Hakkas D, Kaguelidou F, Rey G, Coste J. Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of the French SAGHe study. *J Clin Endocrinol Metab.* 2012;97(2):416–425.
  85. Savendahl L, Maes M, Albertsson-Wikland K, Borgstrom B, Carel JC, Henrard S, Speybroeck N, Thomas M, Zandwijken G, Hokken-Koelega A. Long-term mortality and causes of death in isolated GHD, ISS, and SGA patients treated with recombinant growth hormone during childhood in Belgium, The Netherlands, and Sweden: preliminary report of 3 countries participating in the EU SAGHe study. *J Clin Endocrinol Metab.* 2012;97(2):E213–E217.
  86. Malozowski S. Reports of increased mortality and GH: will this affect current clinical practice? *J Clin Endocrinol Metab.* 2012;97(2):380–383.



87. Rosenfeld RG, Cohen P, Robison LL, Bercu BB, Clayton P, Hoffman AR, Radovick S, Saenger P, Savage MO, Wit JM. Long-term surveillance of growth hormone therapy. *J Clin Endocrinol Metab.* 2012;97(1):68–72.
88. de Lind van Wijngaarden RF, Otten BJ, Festen DA, Joosten KF, de Jong FH, Sweep FC, Hokken-Koelega AC. High prevalence of central adrenal insufficiency in patients with Prader-Willi syndrome. *J Clin Endocrinol Metab.* 2008;93(5):1649–1654.
89. Farholt S, Sode-Carlson R, Christiansen JS, Ostergaard JR, Hoybye C. Normal cortisol response to high-dose synacthen and insulin tolerance test in children and adults with Prader-Willi syndrome. *J Clin Endocrinol Metab.* 2010;96(1):E173–E180.
90. Nyunt O, Cotterill AM, Archbold SM, Wu JY, Leong GM, Verge CF, Crock PA, Ambler GR, Hofman P, Harris M. Normal cortisol response on low-dose synacthen (1 microg) test in children with Prader-Willi syndrome. *J Clin Endocrinol Metab.* 2010;95(12):E464–E467.
91. Takeda A, Cooper K, Bird A, Baxter L, Frampton GK, Gospodarevskaya E, Welch K, Bryant J. Recombinant human growth hormone for the treatment of growth disorders in children: a systematic review and economic evaluation. *Health Technol Assess.* 2010;14(42):1–iv.
92. Colmenares A, Pinto G, Taupin P, Giuseppe A, Odent T, Trivin C, Laborde K, Souberbielle JC, Polak M. Effects on Growth and Metabolism of Growth Hormone Treatment for 3 Years in 36 Children with Prader-Willi Syndrome. *Horm Res Paediatr.* 2010;75(2):123–130.
93. Eiholzer U, Gisin R, Weinmann C, Kriemler S, Steinert H, Torresani T, Zachmann M, Prader A. Treatment with human growth hormone in patients with Prader-Labhart-Willi syndrome reduces body fat and increases muscle mass and physical performance. *Eur J Pediatr.* 1998;157(5):368–377.
94. Feigerlova E, Diene G, Oliver I, Gennero I, Salles JP, Arnaud C, Tauber M. Elevated insulin-like growth factor-I values in children with Prader-Willi syndrome compared with growth hormone (GH) deficiency children over two years of GH treatment. *J Clin Endocrinol Metab.* 2010;95(10):4600–4608.
95. Chernausk SD, Backeljauw PF, Frane J, Kuntze J, Underwood LE. Long-term treatment with recombinant insulin-like growth factor (IGF)-I in children with severe IGF-I deficiency due to growth hormone insensitivity. *J Clin Endocrinol Metab.* 2007;92(3):902–910.
96. Sode-Carlson R, Farholt S, Rabben KF, Bollerslev J, Schreiner T, Jurik AG, Frystyk J, Christiansen JS, Hoybye C. Growth hormone treatment for two years is safe and effective in adults with Prader-Willi syndrome. *Growth Horm IGF Res.* 2011;21(4):185–190.
97. Hoybye C. Inflammatory markers in adults with Prader-Willi syndrome before and during 12 months growth hormone treatment. *Horm Res.* 2006;66(1):27–32.
98. Child CJ, Zimmermann AG, Scott RS, Cutler GB, Jr., Battelino T, Blum WF. Prevalence and incidence of diabetes mellitus in GH-treated children and adolescents: analysis from the GeNeSIS Observational Research Program. *J Clin Endocrinol Metab.* 2011;96(6):E1025–E1034.
99. Cohen P, Germak J, Rogol AD, Weng W, Kappelgaard AM, Rosenfeld RG. Variable degree of growth hormone (GH) and insulin-like growth factor (IGF) sensitivity in children with idiopathic short stature compared with GH-deficient patients: evidence from an IGF-based dosing study of short children. *J Clin Endocrinol Metab.* 2010;95(5):2089–2098.
100. Cabrol S, Perin L, Colle M, Coutant R, Jesuran-Perelroizen M, Le Bouc Y, Czernichow P. Evolution of IGF-1 in children born small for gestational age and with growth retardation, treated by growth hormone adapted to IGF-1 levels after 1 year. *Horm Res Paediatr.* 2011;76(6):419–427.
101. Grugni G, Crino A, Bosio L, Corrias A, Cuttini M, De Toni T, Di Battista E, Franzese A, Gargantini L, Greggio N, Lughetti L, Liviero C, Naselli A, Pagano C, Pozzan G, Ragusa L, Salvatoni A, Trifiro G, Beccaria L, Bellizzi M, Bellone J, Brunani A, Cappa M, Caselli G, Cerioni V, Delvecchio M, Giardino D, Ianni F, Memo L, Pilotta A, Pomara C, Radetti G, Sacco M, Sanzari A, Sartorio A, Tonini G, Vettor R, Zaglia F, Chiumello G. The Italian National Survey for Prader-Willi syndrome: an epidemiologic study. *Am J Med Genet A.* 2008;146(7):861–872.
102. Van Vliet G, Deal CL, Crock PA, Robitaille Y, Oligny LL. Sudden death in growth hormone-treated children with Prader-Willi syndrome. *J Pediatr.* 2004;144(1):129–131.
103. Lindgren AC, Hellstrom LG, Ritzen EM, Milerad J. Growth hormone treatment increases CO(2) response, ventilation and central inspiratory drive in children with Prader-Willi syndrome. *Eur J Pediatr.* 1999;158(11):936–940.
104. Katz-Salamon M, Lindgren AC, Cohen G. The effect of growth hormone on sleep-related cardio-respiratory control in Prader-Willi syndrome. *Acta Paediatr.* 2012;101(6):643–648.
105. Haqq AM, Muehlbauer MJ, Newgard CB, Grambow S, Freemark M. The metabolic phenotype of Prader-Willi syndrome (PWS) in childhood: heightened insulin sensitivity relative to body mass index. *J Clin Endocrinol Metab.* 2011;96(1):E225–E232.
106. Sode-Carlson R, Farholt S, Rabben KF, Bollerslev J, Schreiner T, Jurik AG, Christiansen JS, Hoybye C. Body composition, endocrine and metabolic profiles in adults with Prader-Willi syndrome. *Growth Horm IGF Res.* 2010;20(3):179–184.
107. Brambilla P, Crino A, Bedogni G, Bosio L, Cappa M, Corrias A, Delvecchio M, Di Candia S, Gargantini L, Grechi E, Lughetti L, Mussa A, Ragusa L, Sacco M, Salvatoni A, Chiumello G, Grugni G. Metabolic syndrome in children with Prader-Willi syndrome: the effect of obesity. *Nutr Metab Cardiovasc Dis.* 2011;21(4):269–276.
108. Wysokinski A, Kowman M, Kloszewska I. The prevalence of metabolic syndrome and framingham cardiovascular risk scores in adult inpatients taking antipsychotics - a retrospective medical records review. *Psychiatr Danub.* 2012;24(3):314–322.
109. Goldstone AP, Thomas EL, Brynes AE, Bell JD, Frost G, Saeed N, Hajnal JV, Howard JK, Holland A, Bloom SR. Visceral adipose tissue and metabolic complications of obesity are reduced in Prader-Willi syndrome female adults: evidence for novel influences on body fat distribution. *J Clin Endocrinol Metab.* 2001;86(9):4330–4338.
110. Craig ME, Cowell CT, Larsson P, Zipf WB, Reiter EO, Albertsson WK, Ranke MB, Price DA. Growth hormone treatment and adverse events in Prader-Willi syndrome: data from KIGS (the Pfizer International Growth Database). *Clin Endocrinol (Oxf).* 2006;65(2):178–185.
111. Siemensma EP, de Lind van Wijngaarden RF, Otten BJ, de Jong FH, Hokken-Koelega AC. Pubarche and serum dehydroepiandrosterone sulfate levels in children with Prader-Willi Syndrome. *Clin Endocrinol (Oxf).* 2011;75(1):83–89.
112. Sopher AB, Jean AM, Zwany SK, Winston DM, Pomeranz CB, Bell JJ, McMahon DJ, Hassoun A, Fennoy I, Oberfield SE. Bone age advancement in prepubertal children with obesity and premature adrenarche: possible potentiating factors. *Obesity (Silver Spring).* 2011;19(6):1259–1264.
113. Siemensma EP, Tummers-de Lind van Wijngaarden RF, Festen DA, Troeman ZC, van Alfen-van der Velden AA, Otten BJ, Rotteveel J, Odink RJ, Bindels-deHeus GC, van Leeuwen M, Haring DA, Oostdijk W, Bocca G, Mieke-Houdijk EC, van Trotsenburg AS, Hoorweg-Nijman JJ, van Wieringen H, Vreuls RC, Jira PE, Schroor EJ, van Pinxteren-Nagel E, Willem Pilon J, Lunshof LB, Hokken-Koelega AC. Beneficial effects of growth hormone treatment on cognition in children with Prader-Willi syndrome: a randomized controlled trial and longitudinal study. *J Clin Endocrinol Metab.* 2012;97(7):2307–2314.
114. Miller JL, Lynn CH, Driscoll DC, Goldstone AP, Gold JA, Kimonis V, Dykens E, Butler MG, Shuster JJ, Driscoll DJ. Nutritional phases in Prader-Willi syndrome. *Am J Med Genet A.* 2011;155A(5):1040–1049.
115. Butler MG, Lee PDK, Whitman B. Management of Prader-Willi

- syndrome. 3rd ed. New York: Springer Science Business Media inc.; 2006.
116. Cassidy SB, Schwartz S. Prader-Willi Syndrome. In: Pagon RA, BTDCeale, editor. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993.
  117. Reus L, van Vlimmeren LA, Bart SJ, Otten BJ, Nijhuis-van der Sanden MW. The effect of growth hormone treatment or physical training on motor performance in Prader-Willi syndrome: A systematic review. *Neurosci Biobehav Rev.* 2012;36(8):1817–1838.
  118. Grolla E, Andrighetto G, Parmigiani P, Hladnik U, Ferrari G, Bernardelle R, Dal Lago M, Albarello A, Baschiroto G, Filippi G, Lovato R, Dolcetta D. Specific treatment of Prader-Willi syndrome through cyclical rehabilitation programmes. *Disabil Rehabil.* 2011;33(19–20):1837–1847.
  119. Scheimann AO, Butler MG, Gourash L, Cuffari C, Klish W. Critical analysis of bariatric procedures in Prader-Willi syndrome. *J Pediatr Gastroenterol Nutr.* 2008;46(1):80–83.
  120. Antal S, Levin H. Biliopancreatic Diversion in Prader-Willi Syndrome Associated with Obesity. *Obes Surg.* 1996;6(1):58–62.
  121. Buchwald H. Consensus conference statement bariatric surgery for morbid obesity: health implications for patients, health professionals, and third-party payers. *Surg Obes Relat Dis.* 2005;1(3):371–381.
  122. Marceau P, Marceau S, Biron S, Hould FS, Lebel S, Lescelleur O, Biertho L, Kral JG. Long-term experience with duodenal switch in adolescents. *Obes Surg.* 2010;20(12):1609–1616.
  123. Marinari GM, Camerini G, Novelli GB, Papadia F, Murelli F, Marini P, Adami GF, Scopinaro N. Outcome of biliopancreatic diversion in subjects with Prader-Willi Syndrome. *Obes Surg.* 2001;11(4):491–495.
  124. Papavramidis ST, Kotidis EV, Gamvros O. Prader-Willi syndrome-associated obesity treated by biliopancreatic diversion with duodenal switch. Case report and literature review. *J Pediatr Surg.* 2006;41(6):1153–1158.
  125. Bird S. Capacity to consent to treatment. *Aust Fam Physician.* 2011;40(4):249–250.
  126. De Lourdes LM, Larcher V, Kurz R. Informed consent/assent in children. Statement of the Ethics Working Group of the Confederation of European Specialists in Paediatrics (CESP). *Eur J Pediatr.* 2003;162(9):629–633.
  127. Informed consent, parental permission, and assent in pediatric practice. Committee on Bioethics, American Academy of Pediatrics. *Pediatrics.* 1995;95(2):314–317.
  128. Lau DC. Synopsis of the 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children. *CMAJ.* 2007;176(8):1103–1106.
  129. August GP, Caprio S, Fennoy I, Freemark M, Kaufman FR, Lustig RH, Silverstein JH, Speiser PW, Styne DM, Montori VM. Prevention and treatment of pediatric obesity: an endocrine society clinical practice guideline based on expert opinion. *J Clin Endocrinol Metab.* 2008;93(12):4576–4599.
  130. Australian Government Department of Health and Ageing. Obesity Guidelines. Australian Government Department of Health and Ageing [updated 2009 Jul 31; cited 2011 Aug 31] Available from: URL:<http://www.health.gov.au/internet/main/publishing.nsf/Content/obesityguidelines-index.htm>
  131. Padwal R, Kezouh A, Levine M, Etminan M. Long-term persistence with orlistat and sibutramine in a population-based cohort. *Int J Obes (Lond).* 2007;31(10):1567–1570.
  132. Greenway FL, Dunayevich E, Tollefson G, Erickson J, Guttadauria M, Fujioka K, Cowley MA. Comparison of combined bupropion and naltrexone therapy for obesity with monotherapy and placebo. *J Clin Endocrinol Metab.* 2009;94(12):4898–4906.
  133. Lee MW, Fujioka K. Naltrexone for the treatment of obesity: review and update. *Expert Opin Pharmacother.* 2009;10(11):1841–1845.
  134. Padwal R. Contrave, a bupropion and naltrexone combination therapy for the potential treatment of obesity. *Curr Opin Investig Drugs.* 2009;10(10):1117–1125.
  135. Plodkowski RA, Nguyen Q, Sundaram U, Nguyen L, Chau DL, St Jeor S. Bupropion and naltrexone: a review of their use individually and in combination for the treatment of obesity. *Expert Opin Pharmacother.* 2009;10(6):1069–1081.
  136. Zipf WB, Berntson GG. Characteristics of abnormal food-intake patterns in children with Prader-Willi syndrome and study of effects of naloxone. *Am J Clin Nutr.* 1987;46(2):277–281.
  137. Shapira NA, Lessig MC, Murphy TK, Driscoll DJ, Goodman WK. Topiramate attenuates self-injurious behaviour in Prader-Willi Syndrome. *Int J Neuropsychopharmacol.* 2002;5(2):141–145.
  138. Smathers SA, Wilson JG, Nigro MA. Topiramate effectiveness in Prader-Willi syndrome. *Pediatr Neurol.* 2003;28(2):130–133.
  139. De Waele K, Ishkanian SL, Bogarin R, Miranda CA, Ghatei MA, Bloom SR, Pacaud D, Chanoine JP. Long-acting octreotide treatment causes a sustained decrease in ghrelin concentrations but does not affect weight, behaviour and appetite in subjects with Prader-Willi syndrome. *Eur J Endocrinol.* 2008;159(4):381–388.
  140. Haqq AM, Farooqi IS, O'Rahilly S, Stadler DD, Rosenfeld RG, Pratt KL, LaFranchi SH, Purnell JQ. Serum ghrelin levels are inversely correlated with body mass index, age, and insulin concentrations in normal children and are markedly increased in Prader-Willi syndrome. *J Clin Endocrinol Metab.* 2003;88(1):174–178.
  141. Haqq AM, Stadler DD, Rosenfeld RG, Pratt KL, Weigle DS, Frayo RS, LaFranchi SH, Cummings DE, Purnell JQ. Circulating ghrelin levels are suppressed by meals and octreotide therapy in children with Prader-Willi syndrome. *J Clin Endocrinol Metab.* 2003;88(8):3573–3576.
  142. Tan TM, Vanderpump M, Khoo B, Patterson M, Ghatei MA, Goldstone AP. Somatostatin infusion lowers plasma ghrelin without reducing appetite in adults with Prader-Willi syndrome. *J Clin Endocrinol Metab.* 2004;89(8):4162–4165.
  143. Tzotzas T, Papazisis K, Perros P, Krassas GE. Use of somatostatin analogues in obesity. *Drugs.* 2008;68(14):1963–1973.
  144. Purtell L, Sze L, Loughnan G, Smith E, Herzog H, Sainsbury A, Steinbeck K, Campbell LV, Viardot A. In adults with Prader-Willi syndrome, elevated ghrelin levels are more consistent with hyperphagia than high PYY and GLP-1 levels. *Neuropeptides.* 2011;45(4):301–307.
  145. Sze L, Purtell L, Jenkins A, Loughnan G, Smith E, Herzog H, Sainsbury A, Steinbeck K, Campbell LV, Viardot A. Effects of a single dose of exenatide on appetite, gut hormones, and glucose homeostasis in adults with Prader-Willi syndrome. *J Clin Endocrinol Metab.* 2011;96(8):E1314–E1319.
  146. Eiholzer U, Meinhardt U, Rousson V, Petrovic N, Schlumpf M, L'Allemand D. Developmental profiles in young children with Prader-Labhart-Willi syndrome: effects of weight and therapy with growth hormone or coenzyme Q10. *Am J Med Genet A.* 2008;146(7):873–880.
  147. Buchwald H. Consensus conference statement bariatric surgery for morbid obesity: health implications for patients, health professionals, and third-party payers. *Surg Obes Relat Dis.* 2005;1(3):371–381.
  148. Antal S, Levin H. Biliopancreatic Diversion in Prader-Willi Syndrome Associated with Obesity. *Obes Surg.* 1996;6(1):58–62.
  149. Marinari GM, Camerini G, Novelli GB, Papadia F, Murelli F, Marini P, Adami GF, Scopinaro N. Outcome of biliopancreatic diversion in subjects with Prader-Willi Syndrome. *Obes Surg.* 2001;11(4):491–495.
  150. Papavramidis ST, Kotidis EV, Gamvros O. Prader-Willi syndrome-associated obesity treated by biliopancreatic diversion with duodenal switch. Case report and literature review. *J Pediatr Surg.* 2006;41(6):1153–1158.
  151. Marceau P, Marceau S, Biron S, Hould FS, Lebel S, Lescelleur O, Biertho L, Kral JG. Long-term experience with duodenal switch in adolescents. *Obes Surg.* 2010;20(12):1609–1616.
  152. Scheimann AO, Butler MG, Gourash L, Cuffari C, Klish W. Crit-

ical analysis of bariatric procedures in Prader-Willi syndrome. *J Pediatr Gastroenterol Nutr.* 2008;46(1):80–83.