Recommendations for the Diagnosis and Management of Prader-Willi Syndrome

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Objective: The objective of the study was to provide recommendations for the diagnosis and management of Prader-Willi syndrome throughout the life span to guide clinical practice.

Participants: An open international multidisciplinary expert meeting was held in October 2006 in Toulouse, France, with 37 invited speakers and session chairs (see *Acknowledgments*) and 85 additional registered participants. The meeting was supported by an unrestricted educational grant from Pfizer.

Evidence: Invited participants with particular expertise reviewed the published evidence base for their specialist topic and unpublished data from personal experience, previous national and international PWS conferences, and PWS Association clinical advisory groups. Sessions covered epidemiology, psychiatric, and behavioral disorders; breathing and sleep abnormalities; genetics; endocrinology; and management in infancy, childhood, transition, and adulthood.

Consensus Process: This included group meetings including open discussion after each session. The guidelines were written by the Scientific Committee (authors), using the conclusions provided by the sessions chairs and summary provided by each speaker, including incorporation of changes suggested after review by selected meeting participants (see *Acknowledgments*).

Conclusions: The diagnosis and management of this complex disorder requires a multidisciplinary approach with particular emphasis on the importance of early diagnosis using accredited genetic testing, use and monitoring of GH therapy from early childhood, control of the food environment and regular exercise, appropriate management of transition, consideration of group home placement in adulthood, and distinction of behavioral problems from psychiatric illness. **(*J Clin Endocrinol Metab* 93: 4183–4197, 2008)**

Prader-Willi syndrome (PWS) is a complex multisystem genetic disorder that arises from lack of expression of paternally inherited imprinted genes on chromosome 15q11-q13 (1–5). The syndrome has characteristic phenotypes (6, 7) including severe neonatal hypotonia; early onset of hyperphagia; and development of morbid obesity, short stature, hypogonadism, learning disabilities, behavioral problems, and psychiatric phenotypes with severe consequences and difficult management issues for patients, families, and care givers (6–10). Whereas earlier prevalence estimates in the United States were in the range of 1 in 8,000–20,000, recent epidemiological surveys in Europe and Australia have estimated the lower limit of birth incidence at

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Abbreviations: AHI, Apnea-hypopnea index; BMD, bone mineral density; BMI, body mass index; FISH, fluorescence *in situ* hybridization; FTT, failure to thrive; ID, imprinting defect; OSAS, obstructive sleep apnea syndrome; PWS, Prader-Willi syndrome; SDS, SD score; SRBD, sleep-related breathing disorders; UPD, uniparental disomy.

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around 1 in 30,000, and population prevalence at about 1 in 50,000 (5, 11–13). Recent surveys have highlighted the high rates and varied causes of morbidity and mortality throughout the natural history of the disease (14–16). There is a clear need for an integrated multidisciplinary approach to facilitate early diagnosis and optimize management to improve quality of life, prevent complications, and prolong life expectancy (17).

As the outcome of the recent expert meeting on the comprehensive care of patients with PWS, this paper summarizes clinical practice guidelines, with emphasis on medical and behavioral/psychiatric management, adding to earlier publications also based on accumulated expert opinion (18, 19). Due to space limitations, discussion about education, employment, and social and sexual issues in the management of children and adults with PWS is out of the scope of these current recommendations. Readers are referred to other sources (19).

Diagnostic issues

Although the diagnosis can easily be suspected from well-defined clinical diagnostic criteria, even in the neonatal period, the increasing availability and application of molecular techniques means that genetic testing by an appropriately licensed laboratory is mandatory to confirm the diagnosis.

Over the last 10 yr, the age of diagnosis has fallen significantly and the majority of cases are now diagnosed during the first months of life (17, 20, 21). This should allow the earlier introduction of therapies to reduce the morbidity in particular by preventing obesity. This will not only increase the quality of life for patients but also reduce the burden on the family and care givers.

Definition

PWS arises from the lack of expression of genes on the paternally derived chromosome 15q11-q13. Candidate genes for PWS in this region are physiologically imprinted and silenced on the maternally inherited chromosome (4, 10). PWS develops if the paternal alleles are defective, missing, or silenced. In 75% of cases, there is paternal deletion of chromosome 15q11-q13 (type I or II, depending on the proximal breakpoint) (22, 23), maternal uniparental disomy (UPD) in 24%, and imprinting errors in 1% [due in 15% of cases to either a sporadic or inherited microdeletion in the imprinting center (for review see Ref. 24)], whereas there is a paternal chromosomal translocation in less than 1% of cases.

Genetic testing methods

There are different methods for confirming the diagnosis and identifying the genetic subtype using peripheral blood lymphocytes (25). Because imprinted genes demonstrate differential DNA methylation dependent on parental origin (3, 26), patients with PWS have a maternal-only imprint because they are lacking a paternal contribution. DNA methylation analysis is the only technique, which can both confirm and reject the diagnosis of PWS, and therefore should typically be the initial investigation of choice. This is most commonly done using DNA methylation-specific techniques at the *SNURF-SNRPN* locus (27–29). Parental samples are not required for this analysis. If DNA methylation analysis shows only a maternal pattern, then PWS is confirmed. Further methods may then be performed to determine the genetic subtype and allow appropriate genetic counseling, in particular the recurrence risk.

Fluorescence *in situ* hybridization (FISH) analysis has the advantage of needing only a sample from the proband to detect chromosome 15q11-q13 deletions in PWS (30). High-resolution chromosome analysis will detect only 60% of interstitial chromosome deletions (30). Chromosomal translocations or rearrangements may also be detected using this method. Negative FISH or karyotype analysis does not exclude the diagnosis and so if done first should be followed by DNA methylation analysis. Furthermore, Angelman syndrome can present with neonatal hypotonia, and FISH alone may therefore result in misdiagnosis because it will detect maternal 15q11-q13 deletions.

If subsequent DNA methylation analysis is positive for PWS, then DNA polymorphism analysis should be performed on the proband and parents to distinguish a maternal UPD from an imprinting defect (26, 31). Patients with an imprinting defect (ID) warrant further investigation in a specialized laboratory to determine whether an imprinting center deletion is present (32, 33). Those families with a child with an imprinting center deletion have a recurrence risk of up to 50% if the father of the child is a carrier for the imprinting center deletion (32, 33). The risk of recurrence in case of chromosomal translocations is evaluated up to 10%. In the other groups, the risk of recurrence is the same as the general population.

In the future the new method, methylation-specific multiplex ligation PCR amplification, may be more widely used because it has the advantage of combining dosing and DNA methylation analysis in one assay, thus distinguishing PWS deletions from UPDs and IDs as well as providing an approximate size of the deletion (34).

Genotype-phenotype correlations

There are also several biallelic and maternally expressed, paternally imprinted genes throughout the PWS chromosomal region. Their relative under- or overexpression may explain the increasingly recognized genotype-phenotype correlations, such as differences between type I and II deletions, and between deletion and UPD. In particular hypopigmentation is seen primarily in those with deletion. Patients with UPD have less consistent presence of the characteristic facial phenotype and an increased risk of psychosis (35, 36) but higher verbal intelligence scores and less maladaptive behaviors (37–40), compared with patients with deletions. Intellectual ability, academic achievement, and behavioral and psychological problems appear to be worse in subjects with the larger type I deletion than in type II deletion or UPD (41–45). More work will be needed before we can consider whether and how to translate these differences to individualize the management of patients according to their genotype.

Prenatal diagnosis

A prenatal diagnosis is rarely made, but theoretically it could be suspected in cases of reduced fetal movement and polyhydramnios (46). Genetic testing on samples obtained from chorionic villous sampling and amniocentesis can be performed (47).

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FISH analysis can easily pick up deletions from such tissue, but DNA methylation analysis would be necessary for cases of UPD and IDs. However, the few clinical laboratories doing DNA methylation analysis in a prenatal setting are reluctant to use such chorionic villous sampling samples due to the relevant hypomethylation of this tissue. In the future the introduction of techniques such as comparative array genomic hybridization might be transferred to prenatal diagnosis of PWS due to deletions with resulting ethical implications.

Postnatal diagnosis

There is a marked clinical variability throughout life. The evolving phenotype from birth to adulthood means that the clinical features that should lead to a suspicion of the diagnosis depend on the age of the patient (Table 1). A diagnosis of PWS is particularly helpful during the first months of life and should be thought of in all infants with severe and unexplained hypotonia (48). In addition, the presence of a thin upper lip, almond-shaped eyes, acromicria (short hands and feet), and genital hypoplasia adds to the clinical diagnosis, which should be confirmed by genetic testing. During childhood, a genetic test for PWS should not be performed in every obese child with learning disabilities, but a reduced growth velocity, specific dysmorphic features, and history of neonatal hypotonia are strong pointers to initiate testing. Finally, genetic testing should also be considered in adolescents and adults with a less marked phenotype but behavioral and psychological problems in addition to obesity and delayed or incomplete gonadal maturation. Of note is the fact that the absence of any of the core features of the early phenotype: hypotonia, failure to thrive (FTT) and, in boys, undescended testes, has been found to be associated with negative genetics for PWS (49).

TABLE 1. Indications for DNA testing

Age at assessment	Features sufficient to prompt DNA testing
Birth to 2 yr	Hypotonia with poor suck
2–6 yr	Hypotonia with a history of poor suck Global developmental delay Short stature and/or growth failure associated with accelerated weight gain[a]
6–12 yr	Hypotonia with a history of poor suck (hypotonia often persists) Global developmental delay Excessive eating (hyperphagia, obsession with food) with central obesity if uncontrolled
13 yr through adulthood	Cognitive impairment, usually mild mental retardation Excessive eating (hyperphagia, obsession with food) with central obesity if uncontrolled Hypothalamic hypogonadism and/or typical behavior problems (including temper tantrums and obsessive-compulsive features)

Adapted from Gunay-Aygun *et al.* (7).

[a] This feature has been added by the authors.

Differential diagnosis

Patients with negative testing for PWS should be investigated for other chromosomal deletions and duplications and possible monogenic defects that are associated with PWS or PWS-like features (50–54). Other genetic obesity syndromes, such as Bardet-Biedel and fragile X syndrome, associated with cognitive impairment, can sometimes cause clinical confusion (55). In Bardet-Biedel syndrome, although visual impairment does not usually emerge until 6–8 yr, other phenotypes such as polydactyly (two in three cases), brachydactyly and high arched palate can assist in early diagnosis.

Management of infants

Tube feeding

Historically many neonates and infants were tube fed for more than 2 months because of severe hypotonia and poor suckling resulting in FTT, defined as descent across the centiles of weight or body mass index (BMI). There is no consensus to date on the optimal feeding regimen, whether the use of tube feeding is mandatory or should be used only after intensive and persistent nursing has failed, given the theoretical possibility that it could worsen speech problems. Concerns about the potentially long-term deleterious metabolic and cardiovascular effects of excessive weight gain during the first 2 yr of life in non-PWS infants prompt caution against overfeeding in PWS with FTT (56, 57).

Cryptorchidism

Cryptorchidism is present in over 80% of boys from birth (58, 59). As with non-PWS boys, orchidopexy should be performed ideally during the first or the second year, particularly because there is evidence of both primary and central hypogonadism (58, 59), and rare cases of testicular cancer have been reported in PWS (60). Scrotal hypoplasia and the development of obesity can make surgery difficult if delayed until a later age and could require repeated surgical interventions.

Motor program

Children with PWS have muscular hypotonia, decreased muscle mass, psychomotor delay, and reduced motor activity (61) as well as increased variability in the size of both type I and II muscle fibers, and atrophy of activity-dependent type II fibers has been seen on biopsy (62). Training programs, initiated and supervised by physiotherapists and maintained by parents, have been used for many years without any evidence base (*e.g.* earlier onset of walking) but would seem sensible particularly in combination with GH treatment (see section below). Specific programs may be necessary to counteract the inability of the hypotonic PWS infant to overcome gravity while moving during the early years of life. These years may be a particularly sensitive period for motor development and skill acquisition, which have consequences for cognitive and social development. Although hypotonia improves with age, it does persist into adulthood together with reduced muscle mass, so exercise should be a regular part of daily life.

Speech and language therapy are also important during childhood to help with the impaired articulation and delay in development milestones seen in language acquisition (63, 64).

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Parental guidance

Early diagnosis offers the opportunity for education of parents, families, caregivers, and other health care professionals to receive and give social, psychological, and educational support (17, 18). In addition, support from patient and family associations is increasingly available around the world (www.ipwso.org).

Management of hyperphagia, obesity, and its complications

PWS has been classically described as having two phases: 1) poor feeding and frequent FTT and 2) onset of hyperphagia leading to obesity (8, 65). Phase 1 occurs from birth to early infancy when infants with PWS have central hypotonia and a poor ability to suck and often require tube feeding. Phase 2 is described as beginning between age 1 and 6 yr, usually between 2 and 4 yr (65). Recent examination of the natural history suggests a more complex progression leading to four main nutritional phases with subphases in the first two (66). Not all PWS individuals necessarily go through all the phases and subphases, which may be further altered by the use of GH.

In the first phase, the infant is hypotonic and not obese. Subphase 1a consists of feeding difficulties with or without FTT. In subphase 1b, the infant is growing steadily along a growth curve at a normal rate.

In the second phase, body weight starts to increase. This generally occurs between 18 and 36 months of age. In subphase 2a, the child's weight increases such that it crosses one, two or more weight percentiles without a significant increase in calorie intake or increased interest in food. In subphase 2b, the child increases its daily calorie intake and becomes overweight or obese, with an abnormally increased interest in food, but the appetite is not insatiable and unrelenting as in phase 3.

The onset of phase 3 is quite variable, appearing as early as 3 yr of age or as late as 15 yr. This is the classical phase that most people typically associate with PWS, with aggressive food seeking and a markedly reduced satiety. PWS patients in phase 3 have delayed meal termination and require significantly greater calorie intake, compared with those without PWS, to result in loss of hunger. There is also an early return of hunger after the previous meal with early meal initiation (67). Given free access to food, patients will consume approximately 3 times that of control subjects (68). This occurs despite delayed gastric emptying (69). Abnormalities in the satiety response to food intake in several corticolimbic regions are supported by observations from recent functional neuroimaging studies (70–72).

In phase 4, an individual may still have an increased appetite, but it is not as aggressive and unrelenting as previously observed and seems to occur only in a subset of individuals in adulthood, typically after 30 yr of age.

Neuroanatomical abnormalities have been found in the postmortem hypothalamus from patients with PWS that may underlie the hyperphagia, particularly low oxytocin cell number (10), and structural brain defects are increasingly being recognized in imaging studies that may also contribute to cognitive and behavioral problems (73, 74). In addition, fasting and postprandial plasma levels of the orexigenic stomach-derived hormone ghrelin are greatly elevated in PWS, although they do fall after food intake (75–79). Although somatostatin acutely suppresses plasma ghrelin concentrations in PWS patients, appetite is not reduced (80), whereas a recent study found no benefit of chronic administration of a long-acting somatostatin analog on weight or appetite in PWS (81). Furthermore, levels of the anorexigenic gut hormone pancreatic polypeptide are reduced in PWS (10).

Obesity management involves environmental control with early institution of a low-calorie, well-balanced diet, with regular exercise, rigorous supervision, restriction of access to food and money with appreciation of legal and ethical obligations, and appropriate psychological and behavioral counseling of the patient and family (82–84) (see later discussion under *Ethical issues*). Early discussion with parents about the inevitability of hyperphagia, even during infancy, is essential for attempts to prevent obesity through their ability to set limits and the strict control of the food environment. This should be reemphasized at each visit.

Anecdotally, pharmacological treatment, including available anorexigenic agents, has not been of benefit in treating hyperphagia, although there are few published placebo-controlled studies (8, 10, 82, 85). Study of any potential benefits of newer agents such as endocannabinoid antagonists are awaited in PWS, but recent concerns about psychiatric side effects will need careful monitoring in this group of patients. Restrictive bariatric surgery, such as gastric banding or bypass, have not been shown to reduce hyperphagia or achieve long-term weight reduction and are associated with unacceptable morbidity and mortality (for review see Refs. 86, 87). Whereas some of the reports using biliopancreatic diversion have reported successful weight loss, there were frequent complications from the resulting intestinal malabsorption (86, 87). Importantly, it is unknown whether changes in the food environment might contribute to the outcomes after surgery.

Type 2 diabetes mellitus has been reported in about 25% of adults with PWS with a mean age of onset about 20 yr (88). Although there are no data, it seems logical to approach diabetes management including weight loss and increased exercise, using similar pharmacological agents as with non-PWS obesity-related diabetes, *e.g.* initially insulin-sensitizing agents, such as metformin or thiazolidinediones, with the introduction of insulin as required.

Body composition studies show both increased body fat and reduced muscle in PWS from infancy to adulthood (89–94). Interestingly, magnetic resonance imaging has found a selective relative reduction in visceral adiposity in nondiabetic PWS adults of both sexes (95). This may explain the relative hypoinsulinemia and normal triglyceride levels with preservation of insulin sensitivity and protective elevation in adiponectin levels in patients with PWS, given their overall obesity (79, 95–101). Use of lipid-lowering therapy may therefore be required less than might be expected. Hypertension may be present in up to 38% in adults (102) but is uncommon in children. There are no data on the advantages of particular drugs.

Physical activity in PWS is significantly reduced (103), related to obesity, hypersomnolence, and persistent poor muscle tone. There is a reduced resting metabolic rate relative to body size, related to the abnormal body composition, which further con-

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tributes to a reduction in 24-h energy expenditure (104, 105). Increased physical activity and exercise programs are beneficial in improving body composition in PWS (106).

Deaths in PWS adults are most often obesity related due to cardiorespiratory failure, cor pulmonale exacerbated by obstructive and central apnea, septicemia due to skin infections, and pneumonia and are seen from the teenage years into the 20s, 30s, and beyond (16, 21, 107, 108). Appropriate consultation with cardiologists and pneumologists in severely obese individuals is essential. Use of continuous positive air pressure and nasal intermittent positive pressure ventilation may be beneficial, but oxygen should be used cautiously because of the risk of hypoventilation with reversal of chronic hypoxia (109). Early introduction of graded exercise appears to be a vital part of cardiorespiratory rehabilitation (110).

Recent epidemiological surveys have also emphasized the risks of choking (8% of deaths) due to rapid consumption of food, particularly in patients who are temporarily unsupervised (111), and gastric necrosis and rupture (2% of deaths) from overeating (13, 112, 113). The latter may be present despite the absence of usual clinical signs. Symptoms such as abdominal pain, vomiting, or anorexia warrant detailed and rapid assessment with a low threshold for urgent imaging and surgical exploration.

Growth and GH treatment

Growth and GH status

Mild prenatal growth retardation is common with median birth weight SD score (SDS) of −1.37 (range −2.81 to +0.15), with 20% having SDS less than −2.0, and median birth length SDS of −0.46 (range −2.14 to +1.40) (114). Both premature and postterm deliveries are frequently observed, with delivery more than 3 wk early or late reported in some studies in around one third of cases each (46, 115).

After birth, short stature is almost always present, especially during the second year, because of GH insufficiency exacerbated by the lack of a pubertal growth spurt. In a large multinational cohort of 1135 children with PWS starting GH treatment, median height SDS was −2.2 SDS (−4.1 to −0.3) at a median age of 6.4 yr (1.3–12.9 yr) (115). The serum levels of IGF-I are reduced in the majority of children (116–119) and many adults (120, 121). Spontaneous GH secretion is reduced and GH peak during pharmacological stimulation test is less than 10 μg/liter in 70% of children (122). Adults with PWS have lower stimulated GH secretion than obese controls, but the precise prevalence of severe GH deficiency is unclear because reference ranges are unavailable in severe obesity (121, 123). The experts agreed on the potential importance of knowing the GH status to evaluate differential effects, depending on GH status. In our experience, height velocity does not reflect GH status in children with PWS, particularly when they are obese. Therefore, we agree that prior GH testing is not required before GH treatment but if available may be helpful. Mean spontaneous adult height has been reported as 162 cm in boys and 150 cm in girls (124) and 159 cm in boys and 149 cm in girls (125) in German cohorts.

GH treatment in children

The aims of GH treatment in children with PWS are to improve growth during childhood, adult height, and body composition (for review see Ref. 122). In randomized controlled studies using the currently recommended dose of 1.0 mg/m^2/d, there is a significant increase in height, growth velocity and a decrease in percent body fat during the first year of GH treatment followed by stabilization during the second year. Lean body mass increased significantly during the first two years of GH treatment compared with untreated PWS children (126, 127). After the initial 2 yr, GH therapy for two additional years had continued beneficial effects on body composition when doses of 1.0 and 1.5 mg/m^2·d were administered but not with a dose reduction to 0.3 mg/m^2·d (126). This indicates that maintenance of improved body composition requires at least GH dose of 1.0 mg/m^2·d. Bone mineral density continued to improve at all doses of GH. Only a few studies have reported data on adult height. In the Kabi International Growth Study database, 33 patients (21 boys and 12 girls) reached adult height, and two thirds of them were above −2 SDS; the median adult height was −1 SDS for height after a mean duration of 8.4 yr (114). In a recent report including 21 adults (13 boys, eight girls), the mean adult height was −0.3 SDS for height after a mean duration of 7.9 yr of GH treatment (128). Prior improvements in strength and agility that occurred during the initial 2 yr were sustained, regardless of the GH dose. These improvements during GH treatment might contribute to the higher quality of life and reduced depression (129).

Hypothyroidism has been reported in children with PWS (130, 132–133). It may be of central or peripheral origin, requiring screening with TSH, free T_4, and free T_3 measurements before and on GH treatment. Replacement therapy is recommended if measurements dictate.

The benefits of starting GH treatment as early as 2 yr are well established, but there is increasing evidence of additional benefit in starting therapy between 6 and 12 months of age, particularly in terms of motor development, muscle, head circumference, and possibly cognition (94, 134). Starting GH treatment early could be difficult in the United States where GH treatment is labeled for short stature. In Europe, growth retardation is not required in children with PWS for initiation of GH treatment.

Since October 2002, several reports of unexpected death in infants and children with PWS have been published (for review see Ref. 16). Most of them, whether in patients with or without GH treatment, were related to a complicated course of a relatively mild respiratory tract infection, sleep apnea, adenoid and/or tonsil hypertrophy, hypoventilation, and aspiration or related to obesity. A recent review including 64 children (42 boys and 22 girls, 28 on GH treatment) suggested a high-risk period of death during the first 9 months of GH treatment (16). For this reason it has been advised that GH treatment should be started at a low dose, such as 0.25–0.30 mg/m^2·d or 0.009–0.012 mg/kg·d, increasing during the first weeks and months to reach a standard replacement GH dosage of around 1.0 mg/m^2·d or 0.035 mg/kg·d, monitoring clinical effects, particularly sleep apnea (Table 2), and avoiding high IGF-I levels, particularly if there is a clinical suspicion of overtreatment (edema, worsening or new development of snoring, headache, acromegalic clinical features).

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TABLE 2. Management of GH treatment

	Management monitoring
Before starting GH treatment	Genetic confirmation of PWS
	Evaluation of IGF-I status and, if possible, GH status
	Nutritional evaluation and advice and body composition if available (DEXA)
	Prior control of food environment is vital, especially in obese children
	Complete clinical evaluation including sleep and breathing studies if available. If sleep-disordered breathing, snoring, or enlarged tonsils and adenoids are present, ENT assessment and polysomnography are mandatory
	OGTT, particularly if obese and/or older than 2 yr and family history of diabetes
	Family instruction on GH treatment including benefits and risks of the treatment and importance of careful monitoring
	Scoliosis evaluation including x-ray
	Evaluation of hypothyroidism (TSH, free T_4, free T_3) and commencement of replacement if appropriate
On GH treatment	Regular clinical assessment of height, weight, BMI, body composition, pubertal status, scoliosis, IGF-I, and side effects every 3–6 months
	OGTT if previous impaired glucose tolerance, obese, or family history of diabetes
	Ideally ENT assessment and polysomnography within the first 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
	X-ray $\pm$ orthopedic assessment if concern or doubt about scoliosis
	Regular bone age determination, particularly during pubertal age range
	Monitoring for hypothyroidism
Cessation of GH treatment	Uncontrolled progression of obesity
	Continued worsening of glycemic control despite weight control, diabetic medication, and normal IGF-I
	Continued worsening of sleep-disordered breathing despite weight control, tonsillectomy, and adenoidectomy and normal IGF-I
	Attainment of final height (but because there are potential benefits in adults on body composition, peak bone mass, cognition, and quality of life, reassessment of persistent GH deficiency, and replacement with adult doses may be warranted)

DEXA, Dual-energy x-ray photon absorptiometry; ENT, ear, nose, and throat; OGTT, oral glucose tolerance test.

Sleep-related breathing disorders (SRBD)

A variety of SRBDs has been reported in PWS. Obstructive sleep apnea syndrome (OSAS) may be caused by obesity, sticky saliva, kyphoscoliosis, or adenotonsillar hypertrophy in combination with the narrow upper airways in PWS. Hypotonia of the respiratory muscles may also play a role. Recently, however, it has been demonstrated that nonobese prepubertal PWS children have mainly central sleep apnea and only rarely OSAS during the night (135). The number of central apnea/hypopnea was increased (mean number of five per hour) and did not correlate with BMI. Central sleep apnea indicates a primary disturbance of the central respiratory control mechanism. When children with PWS are overweight, however, half of them have signs of OSAS (136). Arousal and cardiorespiratory responses to rapidly developing hypoxia and hypercapnia are also absent, decreased, and/or delayed in PWS compared with control subjects of similar age, sex, and BMI (137).

OSAS may lead to several complications, such as systemic hypertension, cardiovascular disease, and cor pulmonale. Cor pulmonale plays an important role in the morbidity and mortality of patients with PWS. Rapid eye movement sleep abnormalities and excessive daytime sleepiness are common in PWS and are considered a primary disorder. However, it cannot be excluded that sleep-related breathing disorders disrupt sleep and induce excessive daytime sleepiness as is also found in the general population. In the general population, associations between SRBD and cognition, school performance, and psychiatric and behavioral comorbidities are consistently reported. In individuals with PWS, OSAS is associated with behavioral disturbances, such as autistic-related behavior and impulsiveness (138). A recent study in young PWS infants found that OSAS was associated with lower mental development (139).

Five prospective studies evaluated the effects of treatment with GH on breathing disorders in PWS (136, 140–143). CO_2 responsiveness, resting ventilation, and airway occlusion pressure improved during 6–9 months of GH treatment (140), and the inspiratory and expiratory muscle strength improved during 12 months of GH treatment, compared with controls (141). In a double-blind, placebo-controlled, cross-over study, a decrease in apnea-hypopnea index (AHI) was found after 6 months of GH in 12 PWS children, although the difference, compared with controls, was not statistically significant (142). Another study reported a decrease in AHI after 6 wk of GH in most subjects of a mixed group of adults and children (143). A subset of patients had an increased AHI with more obstructive events after 6 wk of GH, but most of these patients had upper respiratory tract infections and adenoid/tonsil hypertrophy during the second evaluation and two among six had high IGF-I levels. Recently a study in 35 prepubertal PWS children showed that the AHI did not significantly change during 6 months of GH therapy (135). How-

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ever, four children had a marked increase in obstructive apneas during an upper respiratory disease. They continued with GH treatment, and when polysomnography was repeated after recovery, the obstructive apneas had disappeared. In light of these findings, it is suggested that close attention be made to obesity and sleep and breathing problems both before and after commencement of GH treatment, with a low threshold for ear, nose, and throat assessment and polysomnography (Table 2). Due to the high prevalence of sleep-related breathing disorders, sleep studies and ear, nose, and throat evaluation should be performed whenever necessary in these children, regardless of plans for GH treatment.

Orthopedic treatment

Scoliosis is a frequent feature observed in children with PWS with a prevalence of between 30 and 70% (88, 128, 144–146). This high frequency may be explained partly by hypotonia and obesity. Unlike idiopathic scoliosis, young children are often affected with no gender bias. In a report of 139 children (mean age 10 yr), the prevalence was 43%, and particularly high in young ages (15% before 5 yr and 22% between 5 and 10 yr) (146). Scoliosis is frequently associated with kyphosis, particularly in obesity, and both appear to be bad prognostic factors. Weight control is a vital part of its prevention and management. Due to the high frequency of scoliosis, even in infants, spinal x-ray and, if appropriate, orthopedic assessment are mandatory before GH treatment at any age. Regular clinical assessment is required at each visit, whether or not they are receiving GH. Reports of scoliosis worsening during GH treatment may simply reflect its natural history rather than a side effect of treatment in most cases. Cessation of GH is not justified in this situation.

Indications for bracing or surgery are the same as in idiopathic scoliosis. Surgical treatment is indicated in severe early-onset scoliosis-kyphosis and in adolescents near skeletal maturity. Complications are more frequent and severe than in idiopathic scoliosis with a high risk of paraplegia (20%) and of major complications (30%, deep infections, pneumonia, hook out) (147–149). Surgical treatment requires a multidisciplinary team with expertise in the management of scoliosis associated with neuromuscular disease and PWS.

Induction of puberty

Hypogonadism is a consistent feature in both males and females with PWS, and hypogenitalism is present, even at birth. There is increasing evidence to implicate both central and peripheral origins for hypogonadism, at least in males (59). Primate- and testis-specific gene expression has recently been discovered in the PWS chromosomal region (150, 151). Surprisingly, minipuberty, described as gonadotrophin-dependent sex steroid secretion during the first months of life, seems to be present in males (152).

Most individuals will have no or delayed and incomplete puberty. Isolated premature pubarche (probably due to early maturation of zona reticularis of the adrenal gland) has been reported in 14% and precocious puberty in 4% of males and females (58, 153, 154). There is no consensus as to management of either of these conditions. Some investigators have suggested the use of hydrocortisone in premature pubarche to decrease adrenal androgens when there is associated advancement of bone age. Because early puberty is not usually sustained, treatment with GnRH analogs is not needed.

At some stage almost all subjects will require hormonal treatment for induction, promotion, or maintenance of puberty. Mental retardation should not be a contraindication to allow normal pubertal development or preclude sex hormone replacement at any age. Nevertheless, management of hygiene issues in females whose menses are induced should be discussed with the family. There is no consensus as to the most appropriate regimen in PWS. This will be dictated by local availability and experience of different sex steroid preparations, and some investigators have also supported the use of human chorionic gonadotropin in boys (59, 155). Whatever the chosen therapy, the dosing and timing should reflect as far as possible the process of normal puberty. The prevalence of obesity in PWS provides further justification for the use of transdermal and nonsynthetic estrogen preparations, which are usually well tolerated despite skin picking. It remains to be seen whether concerns about aggressive behavior during testosterone replacement are justified and could be better controlled with transdermal testosterone. However, it would seem sensible to initiate and escalate therapy cautiously in boys. Initial low dose of im testosterone preparations (one third to half the recommended dose for hypogonadal adults) with increments as tolerated should be considered when transdermal preparations are not tolerated.

Sex steroids replacement in adults

Hypogonadism is a common but not necessarily universal finding in adults with PWS (58, 59, 121). Primary arguments for using sex steroid replacement in adults with PWS are known benefits to bone health; muscle mass metabolic protection; and possible benefits to mental, emotional, and physical well-being. Estrogen levels in women with PWS may not be as low as postmenopausal levels, perhaps related to aromatization of androgens from excess adipose tissue (95, 156). Testosterone levels in men are often subnormal, although low SHBG levels related to obesity may mean that free testosterone levels are higher than total testosterone levels might indicate (95).

Patients with PWS have low bone mineral density (BMD) and are at risk of osteoporosis, related to deficiencies of sex steroids and GH, and low muscular activity, with elevated biochemical markers of bone turnover (89, 121, 156–159). Reduced BMD in PWS is associated with high risk of fracture in the long bones as well as in the small bones of the hands and feet, with some patients sustaining multiple fractures (88, 148). These findings support the need for hormone therapy, particularly sex steroids replacement, during adolescence. However, neither standardized protocols for the prevention of osteoporosis nor systematic studies of sex hormones treatment in adolescents or adults with PWS are actually available. Estrogen and androgen status should be monitored yearly during adolescence and adulthood and BMD assessed as indicated by dual-energy x-ray photon absorptiometry.

There are few case reports of pregnancy in females with PWS (160, 162). Their cognitive dysfunction, social and emotional immaturity, and the risk of Angelman syndrome in offspring of PWS deletion mothers prompt us to advice against pregnancy.

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Sexual counseling and contraceptive treatment should be used as appropriate. In females with PWS, the use of gonadal hormone replacement should be considered if there is amenorrhea/oligomenorrhea or BMD becomes low-normal in the presence of reduced estradiol levels (158). Administration of testosterone should be considered in men with PWS as for any other hypogonadal subject. Androgen therapy can be more physiologically administered using the new delivery systems of testosterone patches and gel preparations. This avoids the peaks and troughs of injections, which may be of particular interest in PWS because of historical concerns about aggressive behavior with testosterone treatment. Although normal sperm development has been reported in some orchidectomy specimens, there are no reports of paternity in PWS (Klockaert K, Bogaert G, Moerman P, Fryns JP, Vogels A, oral communication, 6th Annual Meeting of the International Prader-Willi Syndrome Organization Conference, Cluj, Romania, 2007).

In conclusion, sex steroid therapy should be ideally minimized and titrated based on individual assessment, BMD, quality of life, sexual and psychosocial issues, acceptability of menstruation, and potential side effects.

Transition into adult life

As with other chronic diseases and disabilities, adolescents with PWS struggle with the move from childhood to adulthood (163). New health care settings and providers, concerns about autonomy, and the changing sexual, psychological, social, and financial environment produce challenges, particularly if disruption of comprehensive care is to be avoided. Furthermore, the behavioral and psychiatric problems and pervasive food seeking specific to PWS add an even higher level of complexity. Nevertheless, health professionals, care givers, patients, and their families should be encouraged that the earlier diagnosis, multidisciplinary care, and use of GH has had significant benefit in reducing morbidity and altering the disease profile at adolescence. It is hoped that in the future, the prevalence of morbid and life-threatening obesity at adolescence will continue to decrease from that seen in historical cohorts. Continuing these benefits into adulthood will require extension of comprehensive care to now involve adult endocrinologists in conjunction with pediatric colleagues, psychiatrists, and medical doctors specialized in persons with intellectual disabilities.

The potential benefits of continuing, starting, or restarting GH treatment after completion of growth are achievement of a normal peak bone mass, continued improvement of muscle mass and strength, reduction of body fat, prevention of cardiovascular morbidity, and improvement in well-being and quality of life (164). National circumstances often dictate cessation of GH treatment and reevaluation of GH status at final height. Personal experience is that body composition can rapidly worsen upon stopping GH at that time, emphasizing the need for formal GH cessation studies. Persistence of GH deficiency (70% partial, 38% severe) and low IGF-I have been reported in many adults with PWS (119, 120).

Modest benefits in body composition, improved cognition, motor performance, and social status have been reported with short-term GH treatment of GH naïve PWS adults using the lower conventional GH dosage (0.53 mg/d) (120). However, such studies may not reflect the outcomes of cessation studies at adolescence. *i.e.* because of differences in baseline phenotype. Reports of other potential benefits of GH in either circumstance are awaited.

Use of transition clinics for chronic endocrine disease may be particularly helpful in the management of adolescents with PWS in this particular period, such as those developed for type 1 diabetes mellitus, Turner syndrome, and childhood-onset GH deficiency.

Management of behavior and psychiatric problems

Before considering the treatment and management of behavioral and psychiatric problems in PWS, it is important to consider what is known about such disorders and specifically the underlying biological and psychological mechanisms. Recent research suggests that the propensity to overeating, repetitive and ritualistic behaviors, and mood disorder may have different etiologies and by implication respond to different treatment approaches and management strategies. The increased propensity to a pattern of behavioral and psychiatric problems that appears specific to PWS cannot be accounted for by some other nonspecific factor such as the presence of intellectual disabilities (165–167). In addition to the universal presence of the propensity to overeating, compulsive and ritualistic behaviors (82, 168), a predisposition to temper outbursts (169), and skin picking are also very common, although not universal. More recently studies of affective disorders and psychiatric illness in people with PWS has found that such disorders (including bipolar disorder) are common in PWS, regardless of genetic subtype, but that prevalence rates of affective psychotic disorder are significantly greater in those with UPD (170). In the population-based study that first reported this (35), all five people with UPD 28 yr old or older had had a psychotic illness, whereas only one of nine with the deletion form of PWS had had a similar illness. Whereas affective disorder in general in PWS is characterized by various degrees of mood fluctuation, which may vary from brief and rapid changes in mood to more prolonged changes in affective state, the psychotic illness is characterized by both auditory hallucinations and persecutory delusions.

Management of temper outbursts and repetitive and ritualistic behaviors

The increased propensity to these behaviors in people with PWS may be as a consequence of developmental arrest (167). The approach is one of management rather than treatment in that the interventions are primarily behavioral with the identification of those factors that predispose, precipitate, or maintain such behaviors. Interventions are then based on the strategies that minimizes the occurrence of such behaviors and most effectively manages them when they do occur. Inconsistent approaches or managements strategies that positively reinforce the unwanted behaviors will only increase the chance that they will occur again in the future. Families and those with PWS therefore need support from psychologists and other professionals to: 1) identify those individual and environmental factors that are associated with an increased risk of or the occurrence of temper outbursts

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or repetitive behaviors; 2) develop management strategies that are informed by these observations; and 3) guide how such strategies can be implemented by family members and others in a consistent and acceptable manner.

Management of affective disorder including affective psychosis

The development of abnormal mood states results from a complex interaction between the biological predisposition and past and present environmental factors that add to such a predisposition and may precipitate its manifestation. Their presentation may not be immediately obvious. A deterioration in the pattern of existing behavior or the onset of new problem behaviors may be markers for an underlying abnormal mood state. This eventually becomes apparent with evidence of fluctuating mood, suicidal thoughts, loss of interest, a deterioration in the ability to concentrate, change in sleep pattern, under- or overactivity, and/or abnormal mental beliefs or experiences. All of these may be of sufficient severity to impact on the person's functional abilities and quality of life. Management and treatment will critically depend both on the diagnosis or not of a mood disorder and on the understanding of the circumstances that have led to the problem developing. The interventions need to consider: 1) factors in the immediate environment (*e.g.* high level of demand, changes in routine) that might have precipitated a change in mood state; 2) the use of medication known to be effective in the treatment of mood disorders and/or psychotic illness; and 3) any other factors that are potentially relevant, such as the effects of any additional medical illness, other phenotypes (*e.g.* sleep disorders), other medications, and/or the impact of life events (such as bereavement) on his/her mental state. In terms of the use of medication, the precise medication or combination of medications that might be used will depend on the comorbid diagnoses made. Where depression is severe, then antidepressant medication may be indicated, and if psychotic symptoms are also present, antipsychotic medication may also be required. There is only limited research available in PWS about the benefits of psychiatric medications for the treatment of psychiatric illness in PWS, but antidepressants and antipsychotic medication may be better than mood-stabilizing medication (161). However, further research is required. Such medications must be given with care, starting on lower-than-normal doses with careful monitoring for adverse events. Whereas medication can help to return a person to a normal mental state and reduce the risk of relapse, it is also important to look to how a predictable, low-stress environment can be maintained and, when the person is able to do so, how any particular issues that may be important in his/her life can be addressed (*e.g.* bereavement, relationships, *etc.*).

Skin picking

Whereas research might indicate that the spectrum of behavioral problems observed in people with PWS have discrete etiologies, there are overlaps. The reason for skin picking in PWS is unclear, but it has been proposed that it is associated with serotoninergic dysfunction and mood. However, approaches to its management will include the use of distraction techniques or the use of activities that are incompatible with skin picking (*e.g.* activities using the hands) and/or medication to stabilize mood as well as other established behavioral techniques. Topiramate has been reported to reduce skin picking in one small open-label study (85). Infections or irritations from any skin lesion themselves will require treatment because such problems may aggravate the skin picking. Crucial to management is the identification of those environmental or individual factors that are associated with skin picking, *i.e.* being unoccupied and bored, an abnormal mood state, or the presence of a preexisting skin lesion.

Other issues

Eyes

Early screening and correction for myopia, hypermetropia, or other eye problems is recommended. Strabismus is also frequent and may require surgery.

Poor salivary production is often observed, which requires parents and child education. Products designed to increase saliva flow (special toothpaste, mouthwash, and sugarless gum) are helpful. Individuals with PWS are less sensitive to thirst and are particularly at risk of dehydration in warm temperatures. Education for regular daily drinking is necessary and could prevent dental complications.

Teeth

Abnormal enamel and frequent caries have been previously reported, but in a recent survey (131), PWS patients presented with a more favorable oral health status than those in previous studies. Orthodontic treatment is often needed and the timing of orthodontia can be complicated by the prolonged growth period.

Ethical issues

The support of people who may be vulnerable, whether in childhood or adult life, requires a careful balance between respecting individual wishes and autonomy, especially in adult life, on the one hand, and on the other, protection from harm, exploitation, or abuse. This is true for many people with intellectual disabilities. However, for people with PWS, there are specific concerns predominantly around the risks associated with overeating and resultant obesity. How these are managed will substantially depend on the cultural context and the laws of any given country.

In childhood once the diagnosis is made and the parents have been helped to understand the particular problem of overeating associated with the syndrome, there is a duty to act in their child's best interests. This will include managing the food environment and limiting access to food. Whereas this may not always be easy, particularly when the wishes of siblings have to be considered, controlling access to food outside the home environment (*e.g.* school) is even more problematic. This becomes even more difficult with increasing age and greater levels of independence, and in adult life, there is a tension between respect for an adult's autonomy to make decisions for him/herself and the severe obesity that is likely to follow with all the health and social consequences.

There is no easy solution to this. However, the following need to be considered. First, those with PWS undoubtedly have an

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TABLE 3. Ideal multidisciplinary team for children and adults with PWS

For children	For adults
Neonatologist	
Medical geneticist[a]	Medical geneticist[a]
Pediatric endocrinologist[a]	Endocrinologist/diabetologist[a]
Neuropediatrician	Gynecologist/urologist[a]
Speech and language specialist	Cardiologist
ENT specialist	
Psychiatrist[a]	Psychiatrist[a]
Orthopedist[a]	Orthopedist[a]
Surgeon (for orchidopexy)	
Pneumologist	Pneumologist
Sleep disorder specialist	Sleep disorder specialist
Dentist	
Ophthalmologist	
Gastroenterologist	Gastroenterologist
Dietitian[a]	Dietitian[a]
Speech therapist	
Physical therapist	Physical therapist
Psychologist[a]	Psychologist[a]
Social worker[a]	Social worker[a]

The coordinator of the multidisciplinary team has traditionally been a specialist in genetics, pediatrics, endocrinology, or learning disabilities. However, the specific individual should reflect the person with the best experience, motivation, team working, and managerial skills, depending on local circumstances. ENT, Ear, nose, and throat.

[a] Those particularly involved in transition.

abnormality of satiety consequent upon their genetic abnormality. The result of this is that they have very limited control over their eating behavior. Second, the nature and severity of this likely abnormality of the feeding pathways is greater than that observed in those with normal obesity. Third, the consequence of uncontrolled access to food is a level of obesity that results not only in very poor health (*e.g.* sleep and respiratory disorders, diabetes mellitus, severe edema, and cellulitis) but also to restrictions on movement and a marked impairment on quality of life. Early death is likely. Fourth, there is emerging evidence that people with PWS benefit from a food-controlled environment in ways that go beyond simply the prevention of obesity. When the food environment is controlled by others and mealtimes and snacks are carefully managed, people with PWS accept this and are then able to focus on different issues in their lives, other than just food.

The main task for families and those providing support is to plan for the possibility of greater independence that comes with adult life and seek to establish support that balances respect for choice and autonomy but still controls access to food and limits and monitors the spending of money. Ideally these strategies have the agreement of the person with PWS and can then be justified on the grounds of consent and the fact that such an approach is clearly in the best interests of the person with PWS. The problems arise when someone, who is now an adult, refuses to agree to such a support package and to limitation on his/her access to food and/or money and decides he/she wants to live independently. In most countries it is for adults to make such decisions for themselves, even if there are likely to be adverse consequences. Should the same general principle of respect for an adult's autonomy apply to people with PWS? One argument against such a view is that people with PWS lack the capacity to make choices about food. Through no fault of their own, the majority of people with PWS do not have the ability to make judgments about when they have eaten enough, and because they remain hungry, even after eating, they are unable to prevent themselves from continuing to eat. If this general principle is accepted, then it can be argued that there is a duty of care, and the task is to work with the person concerned to persuade them to accept living in an appropriately managed environment and if they refused to consider whether there are lawful means whereby the person can be made to live in such an environment. Again, anecdotal evidence is that, once living as such, people with PWS accept it and come to prefer living in a food-controlled environment, even though they may resist such a course of action in the first instance.

Conclusion and future developments

The complex genetics, etiology, multiple phenotypes, and evolving natural history of PWS means that a multidisciplinary professional, parental, societal, and environmental approach to the management is required with many challenges to reducing morbidity and mortality and improving quality of life (Table 3). However, over recent years, an increasing appreciation and availability of important management strategies have already made significant improvements in the life of those with PWS, *e.g.* early diagnosis, use of multidisciplinary teams, introduction of GH treatment, control of the food environment, and better un-

TABLE 4. Major recommendations for the management of PWS

Recommendations
Early diagnosis in infancy using accredited genetic testing should be sought and allows early intervention
Multidisciplinary teams with experience in the management of PWS can provide best practice (Table 3)
Family education and support, early intervention, and individually directed education is vital
Vigorous control of the food environment and regular exercise is essential to manage hyperphagia and obesity
GH therapy should be started early in childhood, taking into account cautions and relative contraindications (Table 2)
Appropriate monitoring of GH replacement is essential (Table 2)
Management of the transition from adolescence to adulthood requires specific attention and care, particularly with regard to patient autonomy and endocrinological issues
Increased availability of group homes with experience in the management of PWS is needed to help placement, quality of life, and health issues in adulthood
Recognition of the distinction between the underlying behavioural problems seen in PWS and acute psychiatric illness is essential

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TABLE 5. Areas of current uncertainty in the management of patients with PWS requiring further study

Areas of current uncertainty
The best age at which to start GH therapy in childhood or infancy
The role for GH therapy in transition and adulthood
The indications and best regimen for sex steroid replacement
The pathophysiology of hyperphagia and hence therapeutic possibilities
The pathophysiology of psychiatric and psychological illness and hence therapeutic possibilities

derstanding of the behavioral and psychiatric aspects (Table 4). Whereas filling of the gaps in our understanding of the underlying science will translate and eventually guide clinical management of PWS (*e.g.* identification of genes and their link to particular phenotypes, genotype-phenotype correlations), several clinical and pathophysiological questions need to be urgently addressed to continue improvement in the care of patients with PWS (Table 5).

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