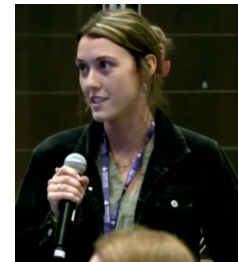


**Prader-Willi Syndrome
Externally-Led Patient Focused Drug Development Meeting (EL-PFDD)
Voice of the Patient Report**



"I am not a scientist, researcher, or doctor. I am not a statistician or in government and public policy. What I am...Who I am...is a parent. A PWS parent.

It is true when they say that 'Being a parent is to have your heart forever walk outside your body.'

Our hearts are burdened with PWS but our minds, our minds are clear- we are focused on treatments.

Thank you for listening, thank you for asking. Thank you for working with our community."

This Externally-Led Patient Focused Drug Development Meeting (EL-PFDD) meeting was organized and hosted by the Prader-Willi Syndrome Association USA (PWSA | USA), the Foundation for Prader-Willi Research (FPWR), and the International Prader-Willi Syndrome Organization (IPWSO). This Voice of the Patient report was prepared as a summary of the input shared by people and families living with Prader-Willi syndrome (PWS) as discussed in-person and virtually on June 22, 2023.

Authors and Collaborators

This report was prepared and submitted on behalf of the Prader-Willi Syndrome Association USA (PWSA | USA) and the Foundation for Prader-Willi Research (FPWR) by: Stacy Ward, CEO, PWSA | USA; Dorothea Lantz, Director of Community Engagement, PWSA | USA, and Theresa Strong, Director of Research Programs, FPWR. PWSA | USA contracted with Tim Turnham, PhD and Rashmika Prakash, MPH from VOZ Advisors, a patient advocacy and engagement consulting firm, for assistance in writing this report. Launa Post of Crowley & Co. attended the EL-PFDD meeting and contemporaneously generated the story boards summarizing comments from participants. We thank James Valentine, JD, MHS, and Larry Bauer, RN, MA for their review of the Voice of the Patient Report.

Disclosures

PWSA | USA and FPWR are tax-exempt, charitable organizations and are eligible to receive tax-deductible contributions under the IRS Code 501(c)(3). The International Prader-Willi Syndrome Organization (IPWSO) is an international non-profit membership organization registered as a charity in England and Wales. These organizations may receive funding from pharmaceutical companies in the form of unrestricted and restricted grants and sponsorship of programs and events.

Funding was received for the Prader-Willi syndrome Externally-Led PFDD meeting from the following sponsors: Soleno Therapeutics , Harmony Biosciences, The EveryLife Foundation, The Steele Family, Acadia Pharmaceuticals

Report Version Date

April 22, 2024

Revision statement

This document was not revised and/or modified in any way after April 30, 2024.

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Point of Contact

For questions related to this report please contact Dorothea Lantz at dlantz@pwsausa.org and Theresa Strong at Theresa.strong@fpwr.org.

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EXECUTIVE SUMMARY

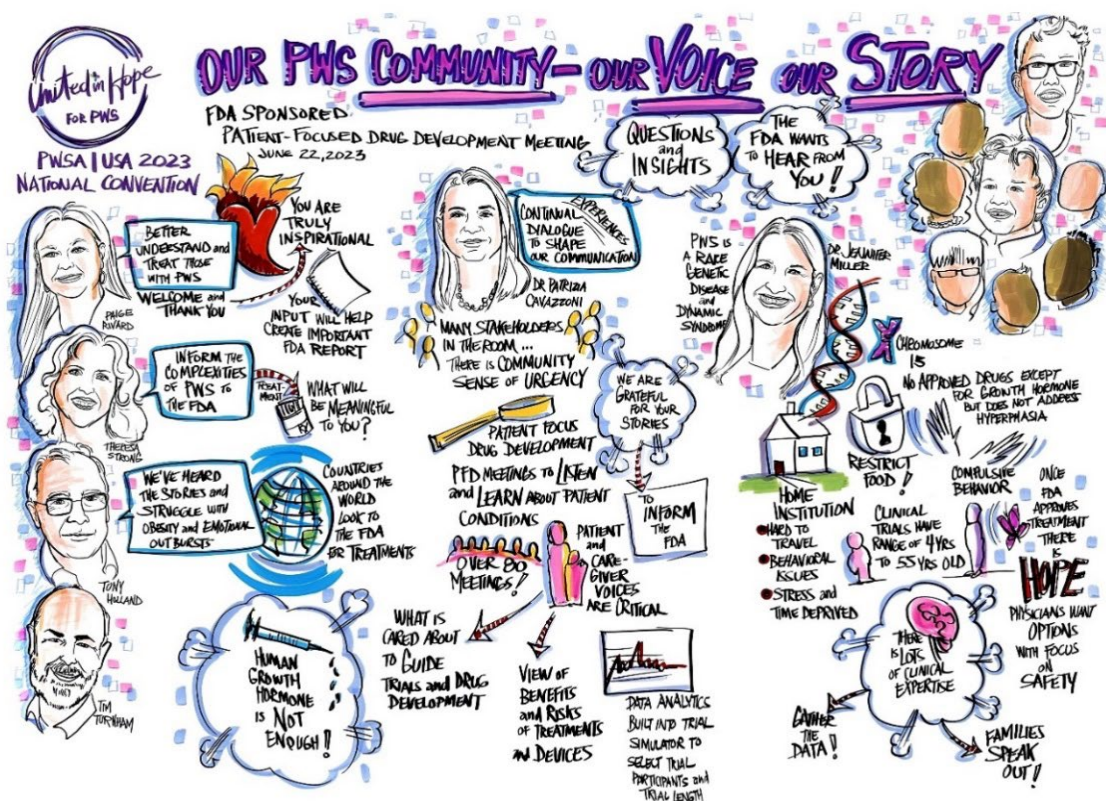
People living with Prader-Willi syndrome (PWS) , their families, providers and others,met for an Externally-Led Patient Focused Drug Development (EL-PFDD) meeting on June 22, 2023, and, through the comments of hundreds of contributors, communicated critical information about the serious and debilitating impacts that represent the reality of living with this disorder, how these unmet needs that impact their daily lives, and their treatment goals for future therapies.

Participants noted that while PWS is characterized by a pervasive drive to eat, hyperphagia, it is a disorder with a wide range of symptoms. Each person with PWS experiences these symptoms in varying severity, and the profile of those symptoms changes with age. The impact of hyperphagia on the lives of those living with PWS is often underestimated, with families of a person with PWS having to make significant life changes to prevent their access to food or anything that can be consumed, often items that would never be considered as “edible”. Constant vigilance is essential, even at night and in settings that most would consider safe, such as the controlled home environment. Beyond hyperphagia, the symptoms most described as impacting daily life were behavioral issues, including anxiousness, skin picking, perseveration, temper outbursts, and sleep disruption. Additional clinical symptoms mentioned, present in some but not all individuals, include scoliosis, gastrointestinal problems, endocrine issues, and seizures. The features of PWS often require overwhelming changes to family dynamics and daily living (e.g., parents taking turns sleeping, taking measure to prevent siblings from suffering emotional or physical harm) and, as a result, often cause tremendous stress on the relationships of those living with PWS and their family members.

The PWS community is desperate for new, effective, disease modifying therapies. Parents noted that even a modest positive improvement in any of the symptoms listed above would lead to meaningful improvements in quality of life. The community also spoke about the inherent risk of untreated PWS, noting the risk of serious injury and the significantly curtailed life expectancy for people with this syndrome. They emphasized that their tolerance for risk is significant when it comes to potential new therapies for PWS, which is due to the significant risk of having no effective treatment.

People impacted by PWS remain committed to helping accelerate the clinical trial process and are hopeful that new treatments will lead to greater opportunities for a more independent life for individuals with PWS.

INTRODUCTION



The EL-PFDD meeting was attended by a variety of stakeholders (including FDA), to hear perspectives from people living with PWS and their caregivers. Dr. Patrizia Cavazzoni, Director of the Center for Drug Evaluation at the FDA, provided a welcome to the meeting via video link, emphasizing the importance of hearing directly from the patient and caregiver community about the impact of PWS and the need for safe and effective therapies. The meeting included observations and insights about the spectrum of challenges associated with PWS, the impact of PWS on daily life, changes that occur over time, and risks associated with untreated PWS. A total of nine caregivers participated in panel discussions, and two patient-speakers provided personal comments. Much of the meeting involved an open forum and discussion among attendees, with dozens of people making comments. PWS community members were also invited to submit written comments through a dedicated [website](#).

This meeting was conducted with guidance from FDA's Patient-Focused Drug Development (PFDD) program, which aims to obtain patient and caregiver perspectives on specific diseases and their treatments through a structured, systematic approach. This report will be made available to the FDA and to the public via the websites of PWSA|USA, FPWR, and IPWSO. More information on the FDA's PFDD program can be found at www.fda.gov/industry/prescription-drug-user-feeamendments/externally-led-patient-focused-drug-development-meetings.

Clinical Overview of Prader-Willi Syndrome

Dr. Jennifer Miller, Professor of Pediatric Endocrinology, University of Florida, provided a clinical overview of the causes, symptoms, and existing treatment for PWS. This rare genetic disorder is caused by the loss of genes expressed on chromosome 15q11-q13. PWS has three main genetic subtypes (paternal deletion [65-75% of cases], maternal uniparental disomy [20-30% of cases], and imprinting defect [1-3%]).¹ People with PWS display a broad range of physical manifestations and disabilities including hyperphagia, sleep issues, hypotonia, obesity, endocrine abnormalities, altered metabolism, gastrointestinal problems, scoliosis, intellectual disability, and behavioral issues (anxiousness, cognitive rigidity, and compulsive behaviors) across the affected individuals' lifetimes.² The complex symptom profile and the fact that symptoms can change over time result in a significant impact on functioning and quality of life. The person living with PWS experiences significant loss of independence and families face high caregiver burden^{3,4}.

PWS typically occurs randomly in individuals with no family history of PWS and is estimated to occur once in about 15,000 to 30,000 births, affecting males and females of all races and ethnicities with equal frequency. The average life expectancy of those with PWS is significantly decreased compared to the general population, with an average age of death of 21 years reported in a recent systematic review of the medical literature⁵. Hyperphagia and obesity are the leading contributors to early death^{5,6}. As a result, there are only approximately 12K known people living with PWS in the United States.

Dr. Miller discussed treatments, highlighting the lack of a cure or disease modifying treatments for PWS. The syndrome is currently managed with restrictions to diet and environment⁷, behavior modification, growth hormone, and other supportive treatments^{1,2}. Significantly, growth hormone replacement therapy is the only FDA-approved therapy for use in children with PWS, though it was only approved to address growth failure, and has no discernable impact on hyperphagia or behavioral challenges. Growth hormone is now routinely used starting in infancy, and has secondary benefits noted by families, researchers, and clinicians (e.g., improved acquisition of gross motor milestones and speech, improved body composition, improved IQ). These added benefits, now critically important to families, were appreciated only after FDA approval allowed growth hormone use to be optimized through widespread clinical use.

The unique symptoms of PWS combined with lack of treatment necessitate constant care and supervision for those with PWS. As symptoms progress, individuals' lives often become more and more restrictive, and their therapeutic needs are dynamic, changing over the course of infancy, childhood, adolescence, and adulthood. Dr. Miller noted that multiple therapeutic options likely will be needed to address the symptoms effectively. Completing clinical trials in PWS is difficult due to, among other aspects, the rarity of the syndrome and behavioral changes as those with PWS age. Still the community is encouraged that therapies can be developed that will result in individuals with PWS having full and possibly even independent lives as adults.

Overview of Panel Discussions

This meeting provided stakeholders with the opportunity to hear directly from people living with PWS and their caregivers about their perspectives on living with PWS and with current treatment approaches and management strategies. The discussion was broken into two sessions.

Session One focused on symptoms and the daily impact of PWS. This session included detailed discussions of the varied and changing nature of symptoms and highlighted the significant benefit of even modest mitigation of one or more symptoms. Session Two addressed current and future treatments including hopes for future treatments. In this session participants expressed frustration

with the current lack of treatment options. They further noted that to date, most clinical trials have not resulted in new, impactful therapies becoming available. The community offered perspectives on improving the clinical trial experience and suggested that additional flexibility in trial design might accelerate and expand current efforts.

Both sessions started with a panel discussion, which was followed by longer facilitated discussion, inviting comments from those in attendance in person and from virtual participants. In addition, two people living with PWS shared their experiences in formal presentations; and others participated during the discussion periods. Some of these comments are reflected in the body of this report. Importantly, however, the people living with PWS who participated in the conference are among the most high-functioning members of this community. Most people with PWS do not have the emotional, behavioral, and/or intellectual capacity to articulate their experiences as clearly as these participants. In some cases, other people with PWS expressed their views and experiences to their parents or siblings, asking that these care partners report on their behalf. Notably, for those unable to express their perspectives, life may be even more challenging than what is described by the people living with PWS who were able to participate in this meeting.

Participants who joined the meeting via live webcast were invited to submit comments throughout the discussion. Additionally, in-person and web participants were asked to respond to polling questions, which provided a sense of the demographic makeup of participants and how many participants shared a particular perspective on a given topic.

More than 200 caregivers and people living with PWS attended the meeting in person, and approximately 100 additional participants attended via webcast. Of those, approximately 120 people provided input through the polling questions. Based on responses to the polling questions, in-person and web participants represented a range of experiences with PWS. Responses included insights on how effective (or not) current treatments are for common PWS symptoms, the current level of impact each symptom has, and the top three health concerns/symptoms that impact daily life the most for the person living with PWS and what symptoms they would most want to see addressed in a new treatment. Full survey responses are provided in Appendix C.

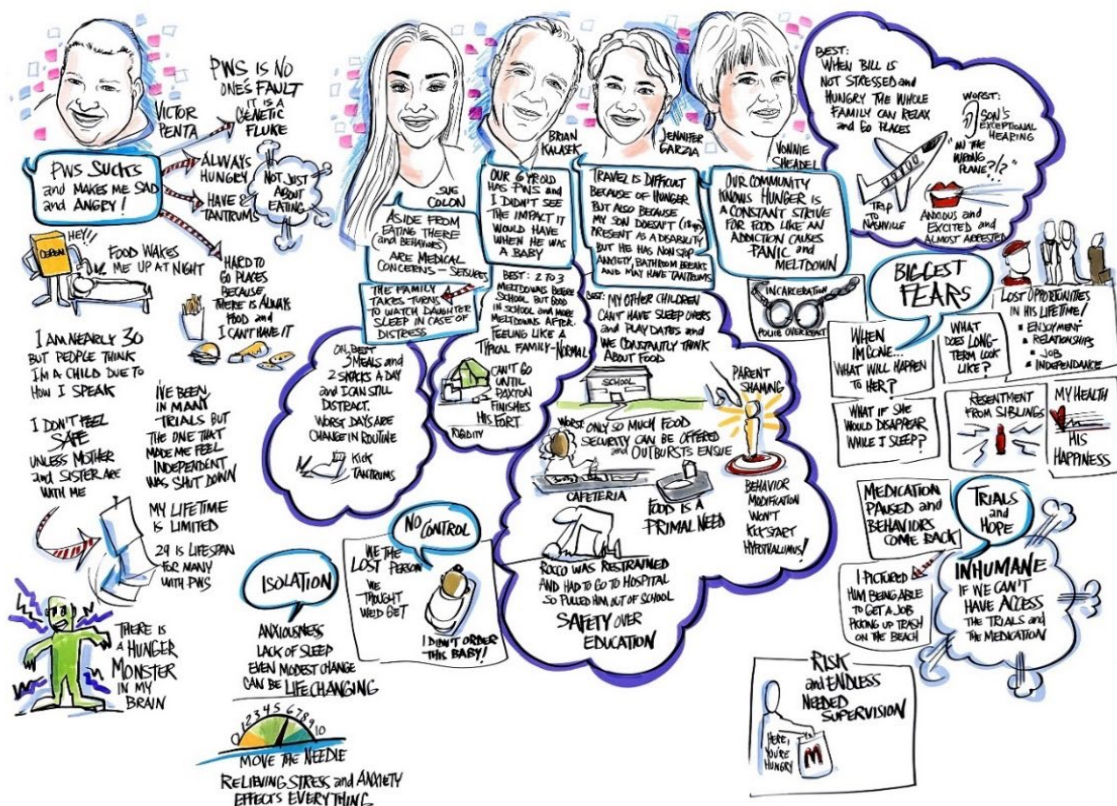
To supplement the input gathered at the meeting, participants and others were encouraged to submit testimonials on the topic. Over 75 testimonials were submitted, the majority by caregivers. As noted above, many testimonials reflect the views of people with PWS who were unable to speak at the meeting. The testimonials were processed by the TREND Community, which used proprietary machine learning systems to derive key themes. That information is included in Appendix D.

More information on the meeting, including the archived webcast recording, is available on the meeting website: <https://www.pwsausa.org/el-pfdd/>.

“My husband and I spend hours on the phone with insurance, panic & parse out medication when there is a shortage and play Tetris with our schedules so that our son can receive private services. We fervently check food labels & scour the internet for recipes, lock our fridge/freezer and pantry, and cover our son with band aids so he doesn’t pick his skin.”

Comment from a PWS parent

Topic 1: SYMPTOMS AND DAILY IMPACT



The first panel discussion focused on the symptoms associated with PWS and how they impact the person with PWS and their families on a day-to-day basis. Symptoms of PWS are varied and change over time. Each person with this syndrome will manifest some or all of these symptoms over the course of their life. These symptoms are connected, pervasive, and have a significant impact on both quality and length of life.

HYPERPHAGIA

The symptom most commonly associated with PWS is hyperphagia, a persistent sensation of hunger associated with an extreme drive to consume food, food related behavioral issues, and lack of normal satiety⁸. A large majority of, but not all, individuals with PWS have this symptom, and it manifests with varying degrees of severity, which can change over time^{2,9}. Even those who are not as significantly impacted live in the fear that their PWS will evolve to include hyperphagia.

The health consequences of hyperphagia are well described and include increased incidence of obesity, pulmonary challenges, cardiovascular disease, injury, and other issues. Hyperphagia-driven obesity is a leading cause of death for people with PWS, with obesity-related pulmonary challenges accounting for as much as a third of early PWS-associated deaths⁵. These issues can be mitigated to some degree by various—albeit challenging—interventions to reduce food access, which is referred to as ‘food security’ in the community. More pressing to the PWS community are other physiological and psychosocial issues driven by hyperphagia. As Victor, a young man with PWS stated, “*Food is*

everywhere". This makes it difficult for a person with PWS to successfully participate in community activities and to focus on other things. As a young woman with PWS commented "*hunger is what the problem is*".

Typically, people with hyperphagia have no ability to ignore food, or anything they may perceive as food. As a result, parents worry about their children with PWS consuming spoiled food, food thrown on the ground or placed in dumpsters or garbage cans, and items that might not even be food—e.g., cigarette butts or medicine. As one parent commented:

"For my son, a cold cup of coffee left on a urinal in a men's room is food. Cough drops are food. A half-eaten sandwich found on the ground. Even pet food or rat poison."

The insatiable search for food and associated inability to discern appropriate vs. inappropriate food items means that people with PWS cannot live independently. Parents know that constant supervision is not normal, and negatively impacts social and emotional development, but feel they have no alternative:

"Our son is a teenager and has never been to a gathering of friends without us being in the room with him. That is not normal or healthy, but what else can we do?"

Adolescent and young adult individuals with PWS talk about the mental health consequences of always having a parent or other responsible adult with them—in school, at gatherings of friends, at birthday parties, sleepovers, sporting events, and concerts. Unlike their peers, they have no agency, no independence. They chafe at these constraints, while also recognizing that they have no other option. As one speaker noted:

"I am 29 years old—the average life expectancy for a person with PWS. I have never been anywhere without the presence of my mother or sister. I know they are there to keep me safe, but I deserve a better life than this."

They talk about wanting—and needing—to live to their full potential and know that the only real hope for this is to have effective treatments to control their food drive. They can envision a life where they are trusted around food and can achieve independence, but this is currently not attainable. In addition to the social isolation, this dissonance results in untenable psycho-social distress.

Food issues are a major barrier to intellectual development. Finding a classroom setting that can accommodate hyperphagia is almost impossible, and parents report that they never feel fully confident that a functioning solution will not suddenly become unsafe due to a change in personnel, the presence of a substitute teacher, or simply moving into a different grade. Parents describe ongoing discussions with school systems over Individualized Education Programs (IEPs). These programs are developed to ensure children with an identified disability attending elementary or secondary educational institutions receive specialized instruction and related services. For people with PWS, however, these and other plans are often inadequate or not followed. Even the best solutions can be faulty:

"My daughter is in a great school and the staff work hard to understand her situation. She is able to be in class with other students because the teacher knows not to expose her to food. Still, a few days ago my daughter was working on a project with a small group of students when she heard the teacher unwrap a cough drop. For her, that was the sound of food and it took an hour for her to re-focus on the project."

The result is an uneven program of education characterized by constant change and upheaval. As another parent commented:

“Food calls to her day and night. She can't have normal friendships because she is sneaking food off their plates at school or playdates. She is aware and hates this about herself!”

Thus, PWS-associated hyperphagia hinders learning, emotional development, the ability to build social networks, and more.

The PWS community feels that the real impact of hyperphagia is not well appreciated. This is not just about hunger, but is, rather, an uncontrollable compulsion to seek food. One panelist emphasized that this life-threatening drive for food is so much more than typical hunger. She noted that without constant supervision and controls, her son's life is on the line, as he might engage in unsafe activities to acquire food. Children have lied, stolen, and snuck away from home so they could access food. One father illustrated it this way:

“I came into our kitchen one morning and just felt something wasn't right. Everything was in its place, but maybe just a bit off. Our refrigerator is locked, as are our cabinets. And we have a video monitor tracking everything that happens in the kitchen. I reviewed the recording and saw my son come into the kitchen in the middle of the night. He moved a chair to the counter, climbed up on the counter and managed to open a top cabinet we didn't think he could reach. He got out some cereal and a bowl and had a big snack. He then cleaned the bowl, replaced the cereal, wiped down the counter, and put the chair back where it had been.”

Hyperphagia also means that people with PWS are easy to victimize. A real concern is children or adults with PWS being lured by food and taken advantage of. The community recounts a story of a young woman who encountered a stranger and has since disappeared. She has never been found. This experience speaks volumes about the level of concern with which parents and care partners live. While no-one in the community endorses a reckless approach to clinical trials, many clinical concerns pale in significance when compared to the risk of eating poison, trading sex for food, or having all sense of self-preservation undermined by the “hunger monster”.

People with PWS report having no control or ability to make different choices. One young adult reflected a common terminology when he said,

“I hate that everywhere I go someone has to be with me. I hate it, but I know it is important to keep me safe from the hunger monster that is in my brain.”

This captures the view of the community—hyperphagia is a “hunger monster” that is stronger than intent, will, or training, and it cannot be ignored. Currently, no treatments are available that are able to keep this “monster” at bay.

BEHAVIORAL ISSUES

While hyperphagia is the symptom most commonly associated with PWS, behavioral issues are also a significant symptom of consequence, and for many people with PWS may be their most troublesome symptom. This is illustrated in Figure 1, a word cloud of other PWS-associated symptoms impacting families. As one speaker noted, *“The first thing I think of when I hear PWS is high anxiety, temper tantrums, physical abuse, stealing.”* Other parents noted that their children display no or only mild hyperphagia but are severely impacted by other symptoms. Parents on the



panel spoke about how PWS-associated behaviors “take over” and mask the positive attributes of their child. Behavioral issues define life within the PWS community. They disrupt family dynamics and social networks, they isolate people living with PWS, interfere with emotional and intellectual development, and significantly increase

Figure 1. Word cloud generated in response to the question: *Aside from hyperphagia, what other PWS symptoms impact your life?*

Sadly, the risk of living with PWS is not limited to hyperphagia. Because many people with PWS present as normal, behaviors such as anxiousness, uncontrolled temper outbursts, and excessive sleepiness can be dangerous, particularly as they move into adolescence and early adulthood.

For young children, concerns driven by behavioral issues center on self-harm—e.g., head-banging as noted above--or harm to others. This may later include harming parents, siblings, friends, and classmates in school. One parent stated that they only wear long-sleeved shirts, to hide the bruises inflicted by their child. They fear their spouse will be accused of domestic abuse if others see the constant presence of these injuries. Other parents talked about watching their children lose friends and of being removed from classrooms or schools because their behavior was uncontrollable. One parent stated,

“I’ve already had to take (my daughter) out of an extended school year program because they couldn’t keep her safe. She’s about to turn just 5 years old and I’ve already had to choose safety or education! My daughter is smart and loves to learn and I had to pull her out of school.”

As these children age through adolescence, they face increasing risk of harm from others. One parent described her concerns with the following:

“Our son was 17 when we started a clinical trial. His behavior, for the first time, became more manageable. He even made it through entire days at school without my having to go get him because of some problem. Then the trial was put on hold and all the old

problems came back. But it was worse because he knew he was not the same and was frustrated that he could no longer control himself. One day things came to a head and he threw a chair. By this time, though, he had turned 18 and was treated by the system as an adult. They handcuffed him and put him in isolation, which only made matters worse. I kept thinking, "What if this happens in public? Will he be seen as a threat and shot? How can I keep him safe now?"

Behavioral issues include the following symptoms:

Anxiousness

Anxiousness is a common theme, but anxiety manifestations vary from person to person, and even change over time. Many PWS symptoms, some of which are described below, are reflections of anxiousness, including perseveration, skin picking, obsessive-compulsive tendencies, and impulsivity¹⁰.

Constant anxiousness is a source of high stress for people with PWS. In addition to the physiological and psychological impact, anxiousness exacerbates social isolation, straining friendships and family ties. When people with PWS talk about living to their full potential they mean, in large part, the ability to build and nurture a network of friends, and to interact with their family in a positive way. For many, anxiousness is perhaps the largest barrier to such interactions.

"I wish I could do more things than I can...going to family outings, my social clubs or sports activities are difficult because food is there. Everything is just hard, because I get stuck, my brain is thinking of food and I don't enjoy my time with friends like I should. I also have tantrums and it's embarrassing when it happens. People stare at me, but I can't stop it. They usually happen because I stole food or my schedule gets changed. But sometimes, it's because I just get really frustrated. When I have one, I really don't remember what I do or say, but I know I feel bad."

As with many PWS symptoms, anxiousness is related to other issues, including hyperphagia. As one parent commented about their 6-year-old child with PWS,

"We're constantly waiting for the hunger to show up. Her anxiety, especially around food, is already rearing its head."

Some meeting participants reported being part of clinical trials that resulted in lowered anxiousness. They found that controlling anxiousness helped the person with PWS control their hyperphagia:

"Our son participated in a study that helped with anxiety. He still had hyperphagia but was better at keeping it at bay. For the first time we had a calm meal at a restaurant. For the first time we saw who our son was meant to be."

The PWS community notes that any therapy that is effective in reducing anxiousness will likely have follow-on impacts on other issues of relevance to individuals with PWS and their families. For example, reduced anxiousness may alleviate perseveration but may negatively increase the ability to manage hyperphagia.

"He has been in 2 clinical trials for hyperphasia that were successful in MY house. The statistical stuff didn't show success, but Bill was not hungry and when he's not hungry, he's not stressed; the whole house is calmer, our extended family is calmer, we can go out to events and it's calmer for everybody everywhere. Everywhere we go is more relaxed...a happier place."

Skin picking

Compulsive skin picking is a common feature in individuals with PWS, with health and social impacts. Some people with PWS have constant open sores because they cannot control this compulsion, or they are bandaged to prevent them from picking at their skin. There can be significant health risks associated with skin picking, including infection, disfigurement, and sepsis. People with PWS may not even be aware they are skin picking, but this can be another factor exacerbating social isolation.

This is particularly true for rectal picking, which can lead to bleeding and, ultimately, to fecal incontinence. People may not be aware they are practicing excoriation, even when they are rectal picking in public. For these people, the action of skin picking is not a conscious choice, but is more aligned with the way hyperphagia works—it is a symptom that controls the patient.

Perseveration

People with PWS are often described as inflexible and may obsess about certain people, objects, or situations. Repeated questions, commenting on the same issue over and over, and requiring that everything be done the same way are common behaviors. One parent described the challenges of *“The constant talking, never listening to what he needs to do....”* People with this manifestation require repeated reassurance yet seem incapable of accepting that reassurance.

Some people, even within the PWS community, refer to this as stubbornness. That terminology, however, implies an intentionality and a level of self-agency that is not typical of a person living with PWS. Perseveration is more like a compulsion—again similar to what is seen in hyperphagia and anxiousness. The person demonstrating perseveration may be aware they are doing so, and that this fixation is not rational, but still be incapable of breaking the fixation in their thinking and behavior.

Temper Outbursts

Individuals with PWS may exhibit temper outbursts, starting in childhood and persisting throughout adulthood⁸. These events may be triggered by unexpected changes in plans or, at times, may come from being denied food:

“The challenges protecting (our son) and others from his food-seeking and rages is something I cannot put into words. The stress is overwhelming and has been ongoing since he was eight.”

One parent reported that her pre-school daughter will bang her head against a hard floor when told she cannot do something. The parents must monitor her constantly to prevent self-harm. The consequences of temper tantrums increase as PWS children age and develop physically. Panelists discussed the challenges of traveling with individuals with PWS, who may have outbursts that disrupt a flight, for example. More than one commentator noted that temper outbursts had led to the police being called, with the potential for catastrophic outcomes. These outbursts impact the entire family, with one parent talking about how the siblings of the person with PWS were not able to have their friends over to their house because of the behaviors. Parents expressed that often people with PWS don't fully understand their anger outbursts or the consequences of those outbursts but do often express regret after an incident.

“Two weeks ago, there was a warning due to a fire in Canada, and we couldn't go outside for her normal playtime because of smoke. That change in routine turned into a full day extravaganza. It went from headbanging, she has a lot of self-injurious behaviors and she's also aggressive towards others. She's only 3 but she bites, kicks, pulls...and that day turned into a whole fiasco. It went from not being able to go outside, to trying to bang her head on the

cement floor, to trying to bite others to taking the dog's cage and being able to throw it across the living room. And she's 3."

SLEEP DISRUPTION

Sleep disruption is a common manifestation of PWS^{11, 12}. Both central sleep apnea and obstructive sleep apnea (OSA) are common. Even parents of young children report having no ability to anticipate when their child will be awake or asleep. This requires constant vigilance, with no "downtime" for caregivers.

"Our daughter is only 3 but she will get out of bed at any hour of the night. My husband and I take turns sleeping so someone is always awake to monitor her."

The nocturnal wakefulness may be tied to the constant feeling of hunger but is also likely the consequence of disruption of circadian rhythm, as has been demonstrated in cell and animal models of PWS. Sleep disruption can manifest as disrupted sleep cycles, as unpredictable periods of wakefulness, and/or as daytime sleepiness. One parent of an adult with PWS notes,

"Throughout the night while her mother sleeps; staff watch over her, wake her to use the bathroom as she is total night incontinent. Redirect her back into her room a number of times any given night."

Over half of individuals participating in the Global PWS Registry report having excessive daytime sleepiness or narcolepsy¹³.

In general, sleep disruption is not well recognized, and this is particularly true within the PWS community. In part this is because many people with PWS have unresolved OSA and struggle with adherence to positive airway pressure therapy. Focus on these issues makes evaluating narcolepsy in people with PWS challenging, with a result that sleep disruption may not be diagnosed in a timely fashion.³ Disrupted sleep can lead to anxiousness, temper management issues, loss of executive function, and other behavioral manifestations. These are attributed to PWS but may actually be driven by—or aggravated by—improper sleep¹⁴.

One parent submitted the following comment:

"My son...has PWS and was almost kicked out of kindergarten and labeled as...emotionally and behaviorally disturbed. I had been trying to figure out his behavior for a few years at this point. Finally, we struck gold — atypical presentation of excessive sleepiness!"

Another parent commented:

"Sleepiness was a constant challenge.... This continued in school – falling asleep in class and gaining weight in spite of our attempts to control it. By middle school, he was easily frustrated by many things and his response was anger. There were no treatments then and even today, treatments are limited. My hope is that today's young families will have treatment options for daytime sleepiness, food issues and behavior."

The health risks of disrupted and inadequate sleep are well known, and include increased incidence of obesity, cardiovascular disease, hypertension, increased anxiety, and depression¹⁵. These track closely with health challenges already faced by people with PWS. Importantly, sleep disruption also results in reduced impulse control, a significant factor given the nature of PWS.

Premature Death

As previously noted, individuals with PWS have a significantly shortened life expectancy. Studies have shown that respiratory issues and hyperphagia are leading causes of early death^{5,6}. Obesity, choking, accidents and sleep apnea all are components of this. Other medical issues impacting mortality are also related to obesity or excessive overeating. In addition, several morbidities arise from the other PWS symptoms, e.g., skin picking, gastrointestinal blockage. Perhaps more significantly, uncontrolled hunger drives people to engage in dangerous activities. Every PWS family has stories to illustrate the risk of food-seeking. These characteristics are evident in an event that was discussed, related to the risk of hyperphagia: A young man slipped out of his home and walked to a nearby fast-food restaurant. He approached someone and told them he was hungry, asking them to buy a meal for him. He did this repeatedly over the course of some hours and ultimately ate, it is reported, eleven full meals. He collapsed and was taken to the hospital where it was determined that his stomach had ruptured with fatal consequences. Analysis of deaths among people with PWS support that this is not an isolated incident¹⁸. Gastric rupture and choking are known hazards during PWS-associated binge eating.

Sadly, the risk of living with PWS is not limited to hyperphagia. Because many people with PWS present as normal, behaviors such as anxiousness, uncontrolled temper outbursts, and excessive sleepiness can be dangerous, particularly as they move into adolescence and early adulthood. During the EL-PFDD meeting, the discussion of safety and risk focused most significantly on considering safety of any new drugs in the context of the risks inherent in living with untreated PWS.

“(Our adult daughter) has no ability to be unattended to care for her own needs. She will elope and consume food.... She will go into her sibling's room and drink his formula given through G tube, she will eat all the toothpaste left out, drink the mouthwash, and even eat non-food items such as bugs or items not made to consume.”

“We live on a busy four-lane road. If our child got away from us and saw a bag from a restaurant in the middle of that road, he would never consider traffic before running out to get it.”

One family reported that their young son was playing in their fenced-in back yard and managed to open the gate. He drove a child's battery-operated vehicle down to the local convenience store, grabbed a handful of snacks, and drove back. They realized he was missing and were frantically looking for him when they saw a long line of cars on the road leading to their house. He was in the middle of a street in the toy car and holding up traffic. Fortunately, the first car that drove up behind him saw what was happening and slowed down before he was hit.

Another parent of an adult with PWS illustrates how anxiousness and compulsive behavior can result in life-threatening situations:

“We had to fly out of town to see my son's PWS specialist, and the boarding gate was one of those “dual” gates that serves two planes. Somehow we boarded the wrong plane. Just as I settled my son down they announced our destination and I realized we were on the wrong plane. I told him we needed to leave, and he panicked. He said, “But I have to see my doctor! I have to see my doctor!” We left the plane but he was yelling and screaming. The gate agent called security and we were met by a group of TSA agents with their hands on their guns. They were shouting commands at my son, which only elevated his anxiousness. I was finally able to get him calmed down, but was petrified about what could have happened to him.”

Topic 1 CONCLUSION

Symptoms of PWS are complex, inter-related, variable, and changing. For example, a recent analysis of data from the Hyperphagia Questionnaire for Clinical Trials showed that hyperphagic behaviors increase over time in people with PWS, unlike the experience of people who do not have PWS⁹. Each person manifests the disorder differently, and the most impactful symptoms can change at any given time¹⁵. This is partly a reflection of age, with manifestations arising over the course of life, but even this is not entirely consistent. The variability in symptom severity across the population and within any given individual makes drug development challenging.

Uncertainty about how PWS symptoms may evolve is constantly in the minds of parents.

“Our daughter is just 1 year old and so far things are manageable. But we know that things will only get harder. My husband and I feel like we are at the bottom of this very large mountain, and we are terrified by what is in front of us.”

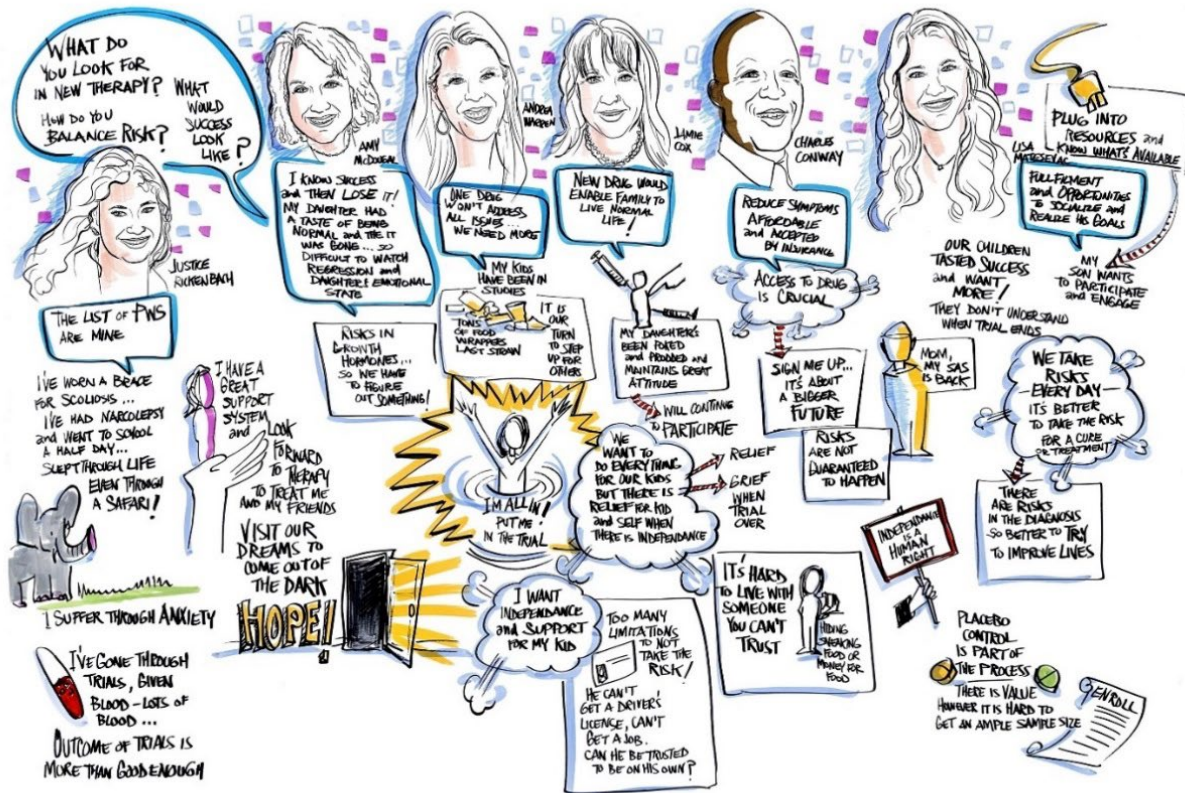
As people with PWS mature and begin to grasp the emerging nature of their symptoms, the sense of helplessness increases. Lack of agency resulting from hyperphagia and anxiousness, described above, is made more exigent by the knowledge that current symptoms may become worse or that other, new symptoms may manifest¹⁶. Quality of life is, thus, reduced by both helplessness and fear of the future.

PWS symptoms may be variable, but they are persistent and pervasive. Caring for a person with PWS requires extraordinary effort and diligence. Neither the person with PWS nor their caregivers can ever lower their vigilance in monitoring and managing these symptoms—even during sleep periods. One lapse can result in major illness or even death, as will be described below. People in the community are desperate for any relief and note that even small improvements in any one symptom has a disproportionately large positive impact on quality of life. As one mother wrote:

“My daughter’s disabilities...have completely isolated us and stopped life from having much quality. I am a single mom unable to work a solid, full-time job due to my daughter’s needs. Resources such as respite don’t work because we aren’t assigned enough hours for anyone to want to help us plus the pay is low. So I am on 24/7. I have not a soul in the world who offers to help me. And I will have no one to care for my daughter when I am gone. I am 51. We survive. That is what we do. One day at a time. There are good days and bad days, but ultimately I cannot give her what she needs and I am a thread away from falling apart.”

The inter-related nature of PWS symptoms is clear and significant, with hyperphagia impacting anxiousness, anxiousness impacting skin-picking, and sleep disruption impacting them all. Issues of cognitive rigidity, and temper outbursts are likely both a physiological manifestation of the disorder and reflection of the extreme psychological strain associated with living with PWS. Regular medical monitoring, and comprehensive support systems are crucial in managing the health of individuals with PWS and mitigating the risk of premature death. Multidisciplinary care teams, including physicians, dietitians, psychologists, and other specialists, play a vital role in addressing the complex needs of individuals with PWS and promoting optimal health outcomes. Importantly, in the minds of the PWS community, because of these connections, an intervention that mitigates one symptom will likely have concomitant benefit for other symptoms and, more importantly, to overall well-being.

Topic 2: CURRENT AND FUTURE TREATMENT



The PWS community expressed frustration that no new and effective therapies have emerged to help manage this syndrome. As indicated by the survey results (Appendix C), and consistent with previous assessments of the PWS community^{15,17} treatments for the most difficult aspects of PWS, including hyperphagia, anxiousness, developmental delay/intellectual disability, and temper outbursts are lacking or largely ineffective. One meeting participant put it this way:

"(Our daughter) is 19 years old. For 19 years we have held out hope that one day there would be a medication available that would make it possible for her to live independently. (She) is very high functioning and she wants what every other young adult wants—independence. Unfortunately, we cannot risk letting her live alone due to the fear that she may literally eat herself to death. Nineteen years old and not one medication has been approved for those who suffer from this cruel and debilitating disease. It wreaks havoc on the individual with PWS and the entire family.

Clinical Trial Experience

There have been more than a dozen clinical trials for PWS in the last decade, and many of those attending the meeting had participated in some of those studies. In discussing clinical trials, several commentators rued what they see as delays and lengthy processes in initiating and conducting the studies. They feel a sense of urgency for new treatments to become available.

Participants noted that having people with PWS participate in clinical trial is challenging. Speakers in both panels commented on the behavioral challenges and difficulties of traveling with an individual

with PWS to clinical trial sites. Any innovations to decrease the number of required patients or reduce the burden on trial participants —while maintaining scientific integrity--would likely lower costs, accelerate timelines, and encourage more activity in this space.

Several speakers commented on the experiences of their loved ones with investigational drugs and how these sometimes did not align with clinical trial endpoints. For example, one parent noted,

“The study drug was amazing at controlling anxiousness, but the goal was to control hyperphagia. Because that goal wasn’t met the study was ended, even though it was really helping.”

Families spoke about how a small improvement in any PWS symptom has an outsized impact on quality of life. They valued the opportunity to experience normalcy and stressed the importance of their loved one with PWS being able to achieve more independence.

Some acknowledged that while the aggregate data for some of the studies did not show benefit, they felt that their individual experience was more positive than the data suggest. As one parent stated,

“For just a few weeks we could see who our child really is, when the symptoms of PWS were made manageable. Now we are back in the fight.”

While acknowledging that the drug development process must be driven by data, for this community their own lived reality is a vital, albeit qualitative, datapoint. Efforts to effectively capture the real-world experience of people in clinical trials and consider the totality of the data were encouraged. As one person expressed it,

“Each person with PWS is an individual with a unique experience; each individual story should be a factor in the decision by the FDA.”

Commentators also expressed disappointment when a trial was ended or put on hold. People reported uncertainty and confusion about the information provided to them by the study sponsors explaining why a study was halted and what the future might be for that drug.

“The trial was ended and we were told we could no longer have access to the drug, even though we were certain it was helping. We don’t know why (the trial) stopped or if it will start up again.”

Several families discussed the impact of seeing progress during a trial, only to have the trial ended or halted. They report children who *“gained 100 pounds”* or *“returned to their old behavior”* when the study drug was no longer available. One particularly poignant comment—*“Once peace has been felt, there should be no going back!”* More effective and transparent communication about such decisions could do much to reduce the angst associated with seeing a drug that appears to be helpful suddenly become unavailable.

Despite some of the challenges and frustrations that the PWS community expressed with respect to clinical trials, many hopeful comments were also shared. Several parents in the room, as well as individuals living with PWS, commented on how their positive experience with an investigational drug had given them reason to be hopeful. They were optimistic that new therapies could be found which would mitigate the challenges associated with PWS and they encouraged persistence in getting clinical trials completed and finding solutions for individuals with PWS.

Tolerance for Risk and Greater Uncertainty of Treatment Benefit

Without exception, people in the PWS community worry about safety for their loved ones from the symptoms of PWS. For them, the real-life safety issues associated with PWS are a factor in their benefit-risk evaluation for trials and potential new treatments. As one parent noted,

“The risk to our children and to our families of doing nothing far outweighs the risk of most side effects, or a medication that doesn’t work for a particular child.”

Importantly, the community is not naïve or incautious about potential toxicities. Rather, they are very clear of the risks inherent in everyday life with PWS so often have a higher risk tolerance for potential side effects of new therapies and for accepting greater uncertainty as to the likelihood of benefit.

These risks are associated with multiple symptoms of PWS are elevated by the fact that many people with PWS present as normal or near normal. They can be charming, bright, and socially engaging, so their PWS symptoms are not seen by the general public through the lens of someone whose behavior is shaped by a disease. As one parent put it,

“(Our son, 19) is very immature for his age. He is outrageously literal, has difficulty with interpersonal relationships, and has an innocence about him that could potentially be dangerous - he has a heart of gold and is no stranger to anyone he meets.”

Behavioral issues place people with PWS at risk of physical harm, and also make them appear threatening to others. Parents see their children having temper tantrums and wonder how they will manage in a few years when that child is likely to be taller, heavier, and stronger than they are. The entire family dynamic is impacted by the introduction of fear. One mother offered this illustration:

“PWS has enormously impacted quality of life for our family, including costing (our older son with PWS) his independence. Our youngest son is now 27 and growing up in a pressure cooker with PWS has resulted in PTSD. Even the mere mention of his brother results in physical and mental distress. We desperately need options.”

Sleep disruption, like hyperphagia and behavioral issues, carries risk in various forms. The health challenges of sleep apnea, sleep disruption, and narcolepsy are noted above. In addition, people with PWS described being accused of drunkenness or drug use because of excessive sleepiness. These incidents have resulted in lost employment, confrontations with members of the public or of law enforcement, and loss of social connections.

Topic 2 CONCLUSION

Interest in clinical trials among the PWS community is very high, driven by poor quality of life for people with this syndrome and their families, by the absence of effective treatment options, and by the high level of risk inherent in the disease. Many individuals reporting experiencing positive treatment benefits from their experience in clinical trials, even if endpoints or final study results did not mirror their personal experience. People who joined the EL-PFDD meeting are cognizant of the challenges with the clinical trial process. They want safe, effective, data-driven solutions; however this needs to be balanced against the risks associated with living with PWS without any effective treatment, which can be deadly. Therefore, they also call for a fresh look at what is meant by “safe” and what is meant by “effective” in the context of PWS. As one person living with PWS said, “I’m all in—sign me up!”

CONCLUSION

The PWS community organized an EL-PFDD meeting in hopes they might provide the FDA, researchers, and drug developers with a deeper, more nuanced understanding of this syndrome. Their comments, survey responses, and submitted statements expressed the incredible complexity and severe life impacts of PWS. They were clear that there is a significant unmet medical need and a desperate need for solutions in the form of new therapies. Patients and their care partners are motivated to participate in clinical trials. They expressed preferences for new therapies that could result in even modest improvement around any of the myriad symptoms evidenced in this syndrome, and to do so in a timely fashion. A sense of urgency was shared by the entire community, and there was a shared sentiment that this urgency should be shared by all stakeholders involved in drug development and review.

“PWS is a spectrum and no matter where your child falls on the spectrum you are affected by it in so many ways. Imagine preparing for battle & doing everything you can to win, knowing that at any given moment you can lose the battle before it even begins. That's what our kids endure--years of therapy to eat, thrive, talk, walk, do things to become independent contributors to society, because they are capable. And out of nowhere, this monster comes in and strips their focus, their ability to concentrate, form relationships, have a normal life because all they can think of is how hungry they are. That is only ONE of the many sides of PWS. I want (my daughter) to have a fruitful life, but we need something to help with the hunger & the MANY other aspects of PWS.”

Q and A and PERSONAL STATEMENTS

MY DAUGHTER WITH SPECIAL NEEDS ADOPTED A CHILD WITH PWS... I DON'T WANT TO FIX THEM BUT SYMPTOMS NEED TO BE MANAGED

I'M CLINICAL PSYCHOLOGIST DAUGHTER HAS PWS AND LUNG DISEASE BUT NOW HAS SEVERAL OTHER DIAGNOSES

INTERVENTION IS AVAILABLE BUT THERE ARE NOT ENOUGH STUDIES. WE HAVE HIGHER THRESHOLD FOR RISK!

PEOPLE ALIVE WITH STAGE 4 CANCER ARE ALIVE TODAY

- I CAN LEAVE HOUSE FOOD UNLOCKED
- TRAVEL
- WAIT FOR FOOD PATIENTLY
- LISTEN TO MY STOMACH
- FEEL FULL BEFORE FINISHING
- CAN STAY HOME ALONE WHEN FOOD IS LOCKED (SOMETIMES EVEN WHEN UNLOCKED)

WE TELL OUR STORIES BUT FEEL HELPLESS BECAUSE THERE ARE NO ANSWERS

NO HELP NO HOPE
19 yrs old
120 lbs
5'8" RIGID and ANTRIM THROWING

MY SON DOESN'T FIT IN PWS CATEGORIES SO HARD TO GET INTO ANY TRIALS

ENCOURAGE OR STEER AWAY FROM MEDICAL INFO FOR CHILD

ONE DAY HE'LL TAKE INTEREST... WE TRY TO MAKE THINGS NOT ALL ABOUT HEALTH AND THERAPIES

HOME MODIFICATIONS

INFORM VISITORS IN ADVANCE OF LOCKED CABINETS SON GETS UPSET IF REMOVED OF THE LOCKS

I CAN'T LIVE WITHOUT THIS DRUG!!!

I WORK and DO LOTS OF ACTIVITIES and I KNOW I CAN BE MORE INDEPENDENT IF NOT OBSESSED OVER FOOD

I HAVE A SHRETT DAUGHTER WHO WISHES EVERYONE WELL BUT I AM TIRED!!! I NEED TO BE MYSELF FOR HER and DO RIGHT FOR ALL THE FAMILIES WITH FAILED TRIALS and HEARTACHE

PWS HAS ROBBED MY SISTER FROM ME UNTIL SHE WAS IN A STUDY

HEY YOU FORGOT TO LOCK THE PRIDE FOR THE FIRST TIME IN THE STUDY WE WERE ABLE TO COMMUNICATE and BOND

GOOD FAMILIES LIVING UNDER UNBEARABLE PRESSURE

SO SAD THAT WE HAVE TO FIGHT FOR SAFETY IN EDUCATIONAL SETTINGS WHEN THERE ARE BEHAVIORAL ISSUES

WE ARE NOT ALONE!

GRATEFUL TO HEAR OTHERS' STORIES
SON TOOK HIS LITTLE ATV OFF PROPERTY TO GO TO STORE
SODA CHIPS and BEER

CHILDHOOD DREAMS CAN BE REALIZED

I WANT MY SISTER TO HAVE A GOOD LIFE and ENJOY A FUTURE and BE ABLE TO HAVE PIZZA

FOOD FOODS... NO FOOD!

SAFETY STANDARDS WILL BE ACCEPTED THAT MIGHT NOT QUALIFY UNDER PAST GOOD STANDARDS

IT'S LIFE OR DEATH

DAUGHTER HAS SUCH HIGH ANXIETY and PULLS OUT HER HAIR

CONSTANT BUZZ LIKE A LOUD, BRIGHT TV IN BACK OF HEAD
ANERY HUNGRY
CAN LEARN and SOCIALIZE WITH THING DENO

QUALITY OF LIFE IS DESERVED!

I'M GOING TO BE A POLICE WOMAN

WEAR LONG SLEEVES TO COVER INFLECTED BRUISES FROM CHILDE BEHAVIOR

FDA PLEASE HELP!

FOOD FOODS... NO FOOD!

CLINICAL TRIAL COMMENTS

WE NEED OPTIONS!
 DO THOUGH MULTIPLE CHOICES ON OUR PATHS, THE TRIALS AND PRODUCTS ARE ALL IMPORTANT

CLINICAL ARMS and END POINTS

TESTING and DETERMINED RESULTS NOT ALL ABOUT HYPERPHAGIA
 DID THE PHARMA CHOOSE / DETERMINE APPROPRIATELY?
 WE NEED PROPER COLLABORATION, SAMPLE SIZES, and THE RIGHT QUESTIONS FOR THE COMPLEXITY OF PMS. SO MUCH NUANCE SO NEED MORE THAN QUESTIONNAIRES



RELAXING FOOD MEASURES
 AGAIN NOT ALL ABOUT HYPERPHAGIA BUT ABOUT THE ANXIETY
 THE DRUG CAN CHANGE EVERYTHING

THIS IS WHAT LIFE WITHOUT PMS IS LIKE... HE CAN GRADUATE and GO TO THE PARTIES...
 STRESS IS RELIEVED FOR HIM, HIS SIBLINGS, and HIS PARENTS

"NORMAL" UNTIL THE TRIAL OVER
 ■ ANXIETY IS BACK
 ■ 100 POUNDS BACK ON
 ■ STRESS and DEPRESSION
 ■ SUICIDAL FEELINGS BECAUSE DOES NOT WANT TO BURDEN FAMILY ANY MORE

TRIALS ARE RIGID — EACH INDIVIDUAL STORY SHOULD INFLUENCE FDA APPROVAL
 THE RESULTS OUTWEIGH THE RISKS
 LIFE IS SO MUCH BETTER
 SO MANY STORIES
 ONCE PAIN HAS BEEN FELT THERE SHOULD BE NO GOING BACK

GIVE THESE KIDS A CHANCE
 AUTHORIZE PMS TREATMENT
 CANCER DRUGS SAME LEVELS
 READ A BOOK WITHOUT HANGING ABOUT FOOD
 I WANT TO GO TO COLLEGE

OUR CHILDREN SHOULD BE AFFORDED THE SAME PROGRESS AS OTHER DEMOGRAPHICS
 THE RIGHT INTERVENTION AT THE RIGHT TIME WILL BRING THE RIGHT OUTCOME

APPROVE THE DRUG

PLEASE GIVE ME MY SON BACK

WE NEED and DESERVE BETTER OPTIONS

NOT ABOUT QUALITY OF LIFE — IT'S ABOUT LIFE!

COMPLEX SYNDROME OF ALWAYS FEELING HUNGRY — LIKE STARVING THAT OVERTAKES THE BRAIN
 DRUG APPROVAL IS THE LIGHT IN THE DARK

MY BABY SISTER CAN'T HAVE PIZZA. SHE HAS A SPECIAL TUMMY

WE NEED TRIALS AT THE INTERNATIONAL LEVEL... THERE IS OPPORTUNITY FOR A BETTER FUTURE

EXERCISE REGULATORY FLEXIBILITY!

LOOK AT THE TOTALITY OF DATA TO APPLY JUDGEMENT OF BENEFIT OVER RISK

AS PARENTS WE NEED TO EXPLAIN and DEMAND

CONTINUE THE CONVERSATION!

OUR KIDS DESERVE BETTER and OPPORTUNITIES TO LIVE LIFE

WE NEED OPTIONS and MEDICATIONS

FDA DRUG APPROVAL



APPENDIX

APPENDIX A: MEETING AGENDA

AGENDA
 Prader-Willi Syndrome
 Externally Led Patient-Focused Drug Development Meeting
 Thursday, June 22nd, 2023
 12:00 PM – 4:30 PM



EL-PFDD Testimonial

12:00 PM	WELCOME, OPENING REMARKS & INTRODUCTIONS Speakers: Paige Rivard, Theresa Strong, Tony Holland, Tim Turnham
12:10 PM	REMARKS FROM CENTER FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD AND DRUG ADMINISTRATION Speaker: Dr. Patrizia Cavazzoni
12:25 PM	CLINICAL FEATURES OF PWS & THERAPEUTIC APPROACHES Speaker: Dr. Jennifer Miller
12:35 PM	DISCUSSION FORMAT OVERVIEW Speaker: Tim Turnham
PANEL 1: SYMPTOMS AND DAILY IMPACT	
12:40 PM	PATIENT SPEAKER SHARES WITH COMMUNITY Speaker: Victor Penta, 29, living with PWS
12:50 PM	AUDIENCE-GENERATED WORD CLOUD <i>menti.com (code: 5832 3856)</i> 
12:55 PM	PANEL DISCUSSION Panelists: Brian Kalasek, Jennifer Garzia, Sue Colon, Vonnie Sheadel
1:30 PM	FACILITATED DISCUSSION
2:20 PM	AUDIENCE POLLING AND BREAK <i>surveymonkey.com/r/pwspfd2023</i> 
PANEL 2: CURRENT AND FUTURE TREATMENT	
2:40 PM	WELCOME BACK AND REVIEW OF POLLING QUESTIONS Speaker: Tim Turnham
2:45 PM	PATIENT SPEAKER SHARES WITH COMMUNITY Speaker: Justice Rickenbach, 19, living with PWS
2:55 PM	PANEL DISCUSSION Panelists: Amy McDougal, Andrea Warren, Charles Conway, Jamie Cox, Lisa Matesevac
3:30 PM	FACILITATED DISCUSSION
4:20 PM	CLOSING REMARKS Speaker: Paige Rivard



APPENDIX B: PANELISTS

All panelists are parents of those living with PWS; their children range in age from two to late thirties.

Panel 1:

Sue Colon

Jennifer Garzia

Brian Kalasek

Vonnie Sheadel

Panel 2:

Charles Conway

Jamie Cox

Lisa Matesevac

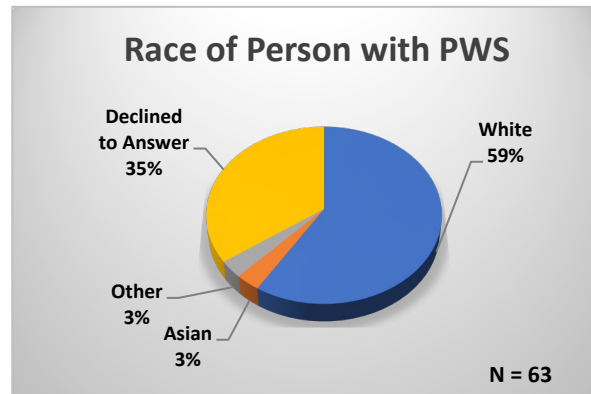
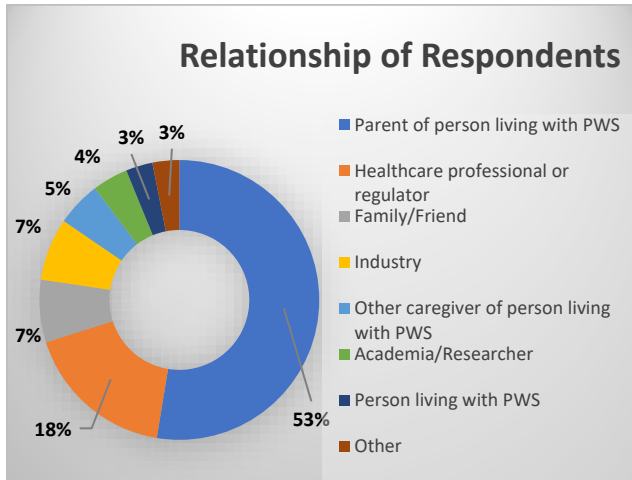
Amy McDougal

Andrea Warren

APPENDIX C: AUDIENCE POLLING QUESTIONS

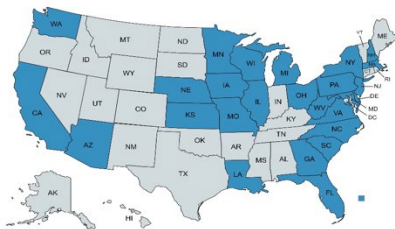
The audience was asked to answer nine questions – five demographic-related, and four PWS-centric. More than 100 people responded to the survey, ranging from 107 to 150 responses depending on the question. Respondents included those present in-person as well as via video conference.

Demographics of Respondents



Age of the Person with PWS	Percent of Respondents
0-4	23%
15-11	21%
12-18	14%
19+	42%

(n=62)

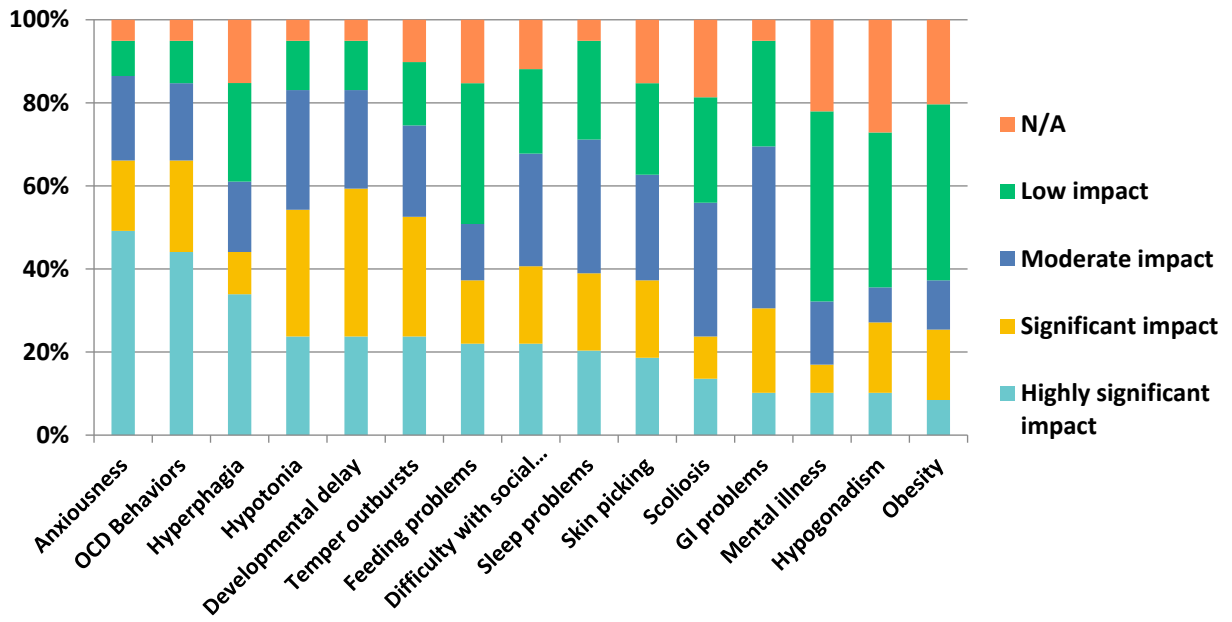


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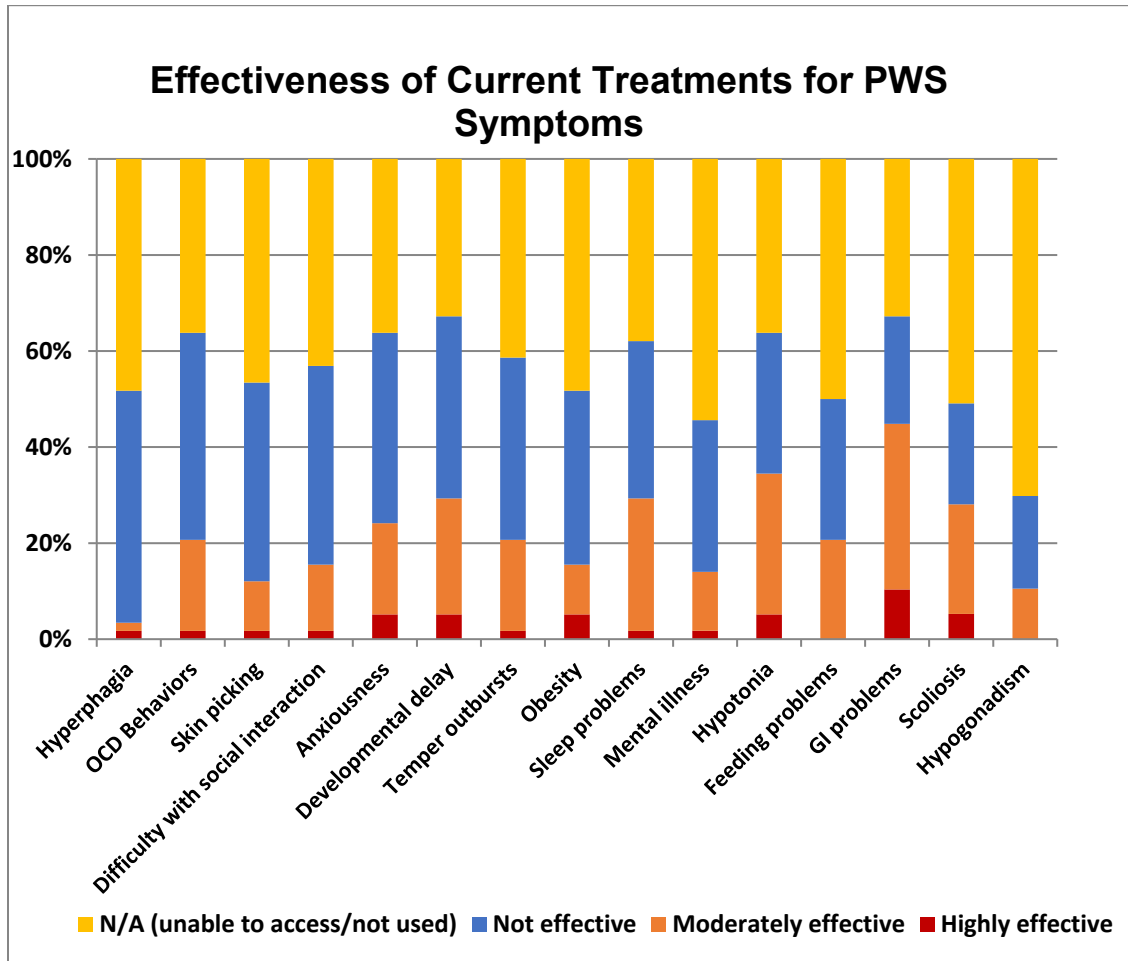
States represented

Response to the question: Please indicate the current level of impact each of the following has on you or the person with PWS you care for (n=59 responses)

PWS Symptoms - Current level of impact



Response to the question: How effective (or not) are current treatments for each of the symptoms listed in the previous question? (n=58)



APPENDIX D: TREND THEME ANALYSIS

The PWS community were invited to submit comments through an online forum. Their entries were reviewed, coded, analyzed, and summarized by TREND Community who identified the following themes:

- **Familial impact**
 - Throughout the feedback, caregivers report that caring for a child with PWS is a challenging journey that takes a toll on the entire family.
 - Some families make adaptations due to the ongoing need to manage food access and intake.
- **Hyperphagia**
 - Hyperphagia is the most referenced symptom of PWS. The constant battle against hunger is articulated as exceptionally challenging.
 - Hyperphagia has been observed as gradually overshadowing the personalities of those living with PWS; creating barriers and constraints despite the existence of innate talents and skills.
- **Sleep**
 - In addition to hyperphagia, sleep is the symptom most referenced. Daytime sleepiness and nighttime sleep challenges are mentioned.
 - Sleep is also identified as a contributing factor to behavioral challenges. This adds to the complexity of understanding and addressing these difficulties, emphasizing the impact on the individuals and their families.
- **Behavioral challenges**
 - Behavioral issues are often stated as challenges that accompany living with and caring for someone living with PWS. Social struggles, immaturity, inflexibility, perseveration, and tantrums are often given as examples.
- **FDA approval process**
 - Caregivers are desperate for approved treatments for hyperphagia, behavioral challenges, and sleep issues.
 - The time-to-approval and failed drug trials are two of the frustrations frequently referenced.
- **Fearful thoughts for the future**
 - The limitations and unknowns about PWS contribute to a sense of fear and concern.
 - The ability to live independently is a big source of concern for many families and caregivers. Additionally, the looming worry of the individual living with PWS having no one to care for them in the future is a heavy burden.
- **Hopeful thoughts for the future**
 - The journey described by these participants reflects a progression from denial and despair to cautious optimism.
 - Despite the challenges, there's a prevailing hope that solutions will be found to help PWS community members thrive and live fulfilling lives. The primary source of this hope stems from new treatment options. This hope often centers on the ability to live independently.

Summary: Living with PWS or serving as a caregiver or family member involves not only navigating complex healthcare systems and facing regulatory hurdles but also requires managing day-to-day emotional, psychological, and behavioral challenges.

Despite the difficulties, concerns, and fears, there is a collective determination to actively find ways to improve the lives of those living with PWS. The resilience demonstrated underscores a commitment to advocacy and the importance of fighting for a future where individuals with PWS can lead productive, independent, full lives.

Acknowledgements: Maria Picone, Lauren Dougherty, and Matt Horsnell from TREND (<https://trend.community/>) performed the analysis and generated the themes.

REFERENCES

1. Angulo, M. A., Butler, M. G., & Cataletto, M. E. (2015). Prader-Willi syndrome: A review of clinical, genetic, and endocrine findings. *Journal of Endocrinological Investigation*, 38(12), 1249-1263. <https://doi.org/10.1007/s40618-015-0312-9>.
2. Driscoll, D. J., Miller, J. L., & Cassidy, S. B. (1998). Prader-Willi Syndrome. In M. P. Adam (Eds.) et. al., *GeneReviews*®. University of Washington, Seattle.
3. Kayadjanian N, Schwartz L, Farrar E, Comtois K, Strong TV. High levels of caregiver burden in Prader-Willi syndrome. *PLoS One*. 13(3):e0194655. doi: 10.1371/journal.pone.0194655, 2018
4. Kayadjanian N, Vrana-Diaz CJ, Bohonowych J, Strong TV, Morin J, Potvin D, Schwartz-Roth L. Characteristics and relationship between hyperphagia, anxiety, behavioral challenges and caregiver burden in Prader-Willi syndrome. *PLoS One*. 2021 16(3):e0248739. doi: 10.1371/journal.pone.0248739.
5. Bellis SA, Kuhn I, Adams S, Mullarky L, Holland A. The consequences of hyperphagia in people with Prader-Willi Syndrome: A systematic review of studies of morbidity and mortality. *Eur J Med Genet*. 65:104379, 2022. doi: 10.1016/j.ejmg.2021.104379.
6. Butler MG, Manzardo AM, Heinemann J, Loker C, Loker J. Causes of death in Prader-Willi syndrome: Prader-Willi Syndrome Association (USA) 40-year mortality survey. *Genet Med*. 2017 Jun;19(6):635-642. doi: 10.1038/gim.2016.178. Epub 2016 Nov 17.
7. Miller JL, Tan M. Dietary Management for Adolescents with Prader-Willi Syndrome. *Adolesc Health Med Ther*.11:113-118. doi: 10.2147/AHMT.S214893. eCollection 2020
8. Schwartz , L., Caixàs, A., Dimitropoulos, A., Dykens, E., Duis, J., Einfeld, S., Gallagher, L., Holland, A., Rice, L., Roof, E., Salehi, P., Strong, T., Taylor, B., & Woodcock, K. (2021). Behavioral features in Prader-Willi syndrome (PWS): Consensus paper from the international PWS clinical trial consortium. *Journal of Neurodevelopmental Disorders*, 13(1). <https://doi.org/10.1186/s11689-021-09373-2>.
9. Matesevac, L., Vrana-Diaz, C. J., Bohonowych, J. E., Schwartz, L., & Strong, T. V. (2023). Analysis of hyperphagia questionnaire for clinical trials (HQ-CT) scores in typically developing individuals and those with Prader-Willi syndrome. *Scientific Reports*, 13(1). <https://doi.org/10.1038/s41598-023-48024-5>.
10. Singh, D., & Mozdzer, E. (2022). Anxiety in Prader-Willi syndrome. *Neuro-behavioral Manifestations of Prader-Willi Syndrome*, 41-57. <https://doi.org/10.1017/9781108886727.007>
11. Ingram, D. G., Arganbright, J. M., Paprocki, E., & Halpin, K. L. (2022). Sleep disorders in children with Prader Willi syndrome: Current perspectives. *Nature and Science of Sleep*, 14, 2065-2074. <https://doi.org/10.2147/nss.s361518>.
12. Itani, R., Gillett, E. S., & Perez, I. A. (2023). Sleep consequences of Prader-Willi syndrome. *Current Neurology and Neuroscience Reports*, 23(3), 25-32. <https://doi.org/10.1007/s11910-023-01254-6>.
13. Shelkowitz E, Gantz MG, Ridenour TA, Scheimann AO, Strong T, Bohonowych J, Duis J. Neuropsychiatric features of Prader-Willi syndrome. *Am J Med Genet A*.188:1457-1463, 2022. doi: 10.1002/ajmg.a.62662.

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14. Choong, C. S., Nixon, G. M., Blackmore, A. M., Chen, W., Jacoby, P., Leonard, H., Lafferty, A. R., Ambler, G., Kapur, N., Bergman, P. B., Schofield, C., Seton, C., Tai, A., Tham, E., Vora, K., Crock, P., Verge, C., Musthaffa, Y., Blecher, G., ... Downs, J. (2022). Daytime sleepiness and emotional and behavioral disturbances in Prader-Willi syndrome. *European Journal of Pediatrics*, 181(6), 2491-2500. <https://doi.org/10.1007/s00431-022-04439-2>.
 14. Institute of Medicine, Board on Health Sciences Policy, & Committee on Sleep Medicine and Research. (2006). *Sleep disorders and sleep deprivation: An unmet public health problem*. National Academies Press.
 15. Tsai, J., Scheimann, A. O., McCandless, S. E., Strong, T. V., & Bridges, J. F. (2018). Caregiver priorities for endpoints to evaluate treatments for Prader-Willi syndrome: A best-worst scaling. *Journal of Medical Economics*, 21(12), 1230-1237.
 16. Dykens EM, Roof E, Hunt-Hawkins H. 'The cure for us is a lot of things': How young people with Prader-Willi syndrome view themselves and future clinical trials. *J Appl Res Intellect Disabil*. 2022 Mar;35(2):460-470. doi: 10.1111/jar.12950
 17. Summary of the Impact of PWS on Individuals and Their Families and Views on Treatments: Results of an International Online Survey: <https://www.fpwr.org/pws-patient-voices>
 18. Stevenson, D. A., Heinemann, J., Angulo, M., Butler, M. G., Loker, J., Rupe, N., Kendell, P., Cassidy, S. B., & Scheimann, A. (2007). Gastric rupture and necrosis in Prader-Willi syndrome. *Journal of Pediatric Gastroenterology and Nutrition*, 45(2), 272-274. <https://doi.org/10.1097/mpg.0b013e31805b82b5>.