



# Externally-Led Patient Focused Drug Development (EL-PFDD) meeting on Phelan-McDermid Syndrome

November 8, 2022

**Meeting hosted by:** CureSHANK

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## Phelan-McDermid Syndrome Voice of the Patient Report

The CureSHANK mission is to accelerate the development of treatments for Phelan-McDermid Syndrome and SHANK related disorders. This *Voice of the Patient* report was prepared on behalf of CureSHANK as a summary of the input shared by families and caregivers living with Phelan-McDermid Syndrome (PMS) during an Externally-Led Patient Focused Drug Development (EL-PFDD) meeting, conducted virtually on November 8, 2022.

**Authors and Collaborators:** This report was prepared and submitted on behalf of CureSHANK and PMSF by, Geraldine Bliss, Founder and President, CureSHANK and by Chrystal Palaty, medical writer.

Consulting Partners include James Valentine, Esq. and Larry Bauer, RN, MA, from Hyman, Phelps & McNamara, P.C.

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James Valentine, Esq. and Larry Bauer, RN, MA are employed by Hyman, Phelps & McNamara, P.C., a law firm that represents patient advocacy organizations and companies that are developing therapeutics and technologies to advance health.

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**Point of Contact:** Please contact Geraldine Bliss ([connect@cureshank.org](mailto:connect@cureshank.org)) for questions related to this report.

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We also wish to thank the representatives from advocacy and professional organizations, pharmaceutical companies, federal agencies and universities from across the world who also took the time to attend our meeting. We want to especially thank the basic and translational investigators working in labs all around the world whose work has led to a solid foundation of science that is now resulting in clinical trials already in progress and being planned for the near future. We hope and expect this meeting will encourage future research and successful new product development for people living with PMS who urgently need treatment options.

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## Executive Summary and Key Meeting Insights

CureSHANK, along with its co-planning partner, the Phelan-McDermid Syndrome Foundation (PMSF) hosted the Phelan-McDermid Syndrome Externally-Led Patient Focused Drug Development (EL-PFDD) meeting on November 8, 2022. This meeting was held to provide a patient and caregiver perspective of the symptoms and burdens associated with Phelan-McDermid Syndrome (PMS) in daily life, as well as the massive unmet treatment needs experienced by families who live with PMS every day. The meeting was held virtually to enable as many community members to participate as possible and to allow many different voices to be heard.

This EL-PFDD meeting was modeled after the work of the FDA's Patient Focused Drug Development (PFDD) initiative. PFDD is a systematic way of gathering patient perspectives on their condition and on available treatments. The information gathered at the meeting is presented in this *Voice of the Patient* report, a high-level summary of the perspectives generously shared by the families and caregivers of individuals living with PMS, who participated in the November 8, 2022, EL-PFDD meeting. The report also includes selected comments that were submitted through an online portal.

The information in the *Voice of the Patient* report may be used to guide therapeutic development and inform the FDA's benefit-risk evaluations when assessing therapies to address PMS. The hope is that this information will catalyze better treatments and ultimately a cure for all those affected by PMS.

CureSHANK has provided this report to the FDA, government agencies, regulatory authorities, medical products developers, academics, and clinicians, and it is publicly available for the many stakeholders in the PMS community. The input received from the November 8, 2022, EL-PFDD meeting reflects a wide range of PMS experiences, however not all symptoms and impacts may be captured in this report.

## Key meeting insights

- 1. Phelan-McDermid syndrome is a complex syndrome characterized by intellectual disability.** PMS is characterized by a wide range of abilities and disabilities, with the type and severity of symptoms varying from one person to another. Individuals living with PMS often have a complex and interrelated constellation of symptoms.
- 2. Regression is a common characteristic of PMS.** Children may lose many acquired skills including communication. While triggers of regression in PMS are not fully understood, older patients often experience regression after psychiatric episodes.
- 3. Developmental delay and intellectual impairment are top health concerns followed by communication issues and muscle weakness.** Most children with PMS do not have speech and therefore are unable to tell their own stories, advocate on their own behalf, or describe if they are in pain. Many have behavioral difficulties that lead to social isolation for

themselves and their families. Some are severely affected by psychiatric illness, anxiety, obsessive-compulsive disorder (OCD), bipolar disorder or schizophrenia, and some experience epilepsy. Low muscle tone (or hypotonia), high pain tolerance, feeding difficulties, sleep problems, body temperature regulation, gastrointestinal problems, and dysmorphisms are but a few of the PMS-related health concerns that further diminish health related quality of life. Some have even lost their lives as a direct consequence of these PMS-related manifestations.

4. **PMS has severe quality of life impacts on those living with the disease, as well as on parents and siblings.** Most activities of daily life, including communicating needs or wants, self-care (bathing, dressing, toileting) and socializing with peers/siblings are affected. Most individuals living with PMS rely on their parents and caregivers for all their daily needs, and many require 24-hour care. Hospitalization is frequent for individuals with PMS. A lack of spatial and safety awareness can lead these children to danger; some parents rely on monitoring and security measures to keep their children safe. Some families have developed strategies to cope with the symptoms and impacts of PMS in daily life.
5. **PMS has an overwhelming unmet medical need.** There are no FDA approved treatments for PMS despite its severely debilitating manifestations. Parents and caregivers are open to trying almost anything to try to relieve their child's suffering; most have tried an incredibly high number of treatments and approaches for symptom management, with very little success. Some received medications that caused more harm than good.
6. **Patients require a lot of different therapeutic approaches.** Most individuals with PMS start receiving therapeutic interventions early in their childhood and continue throughout their lives. Therapeutic approaches of speech, occupational and physical therapy are at the top of the list.
7. **Existing therapies and medical treatments are not very effective.** They only address some, but not all of the symptoms, and many medications have side effects. Regression further negates the benefits achieved from therapy.
8. **Parents and caregivers have many worries for their loved ones, especially about their future care.** They worry that their loved ones will be completely dependent on caregivers, that symptoms will only get worse, and their loved ones will be unable to communicate their health problems. Many parents fear losing their child prematurely.
9. **Parents identified their top priorities for benefits that new therapies could deliver.** These included improved cognitive functioning, improved communication, and preventing or slowing regression.

## Introduction and Meeting Overview

### Clinical overview of Phelan-McDermid syndrome<sup>1</sup>

Phelan-McDermid syndrome (PMS) is an intellectual disability syndrome which profoundly impacts the quality of life of affected patients and their families. It is a rare genetic disorder caused by pathogenic changes to the *SHANK3* gene, most commonly deletions, unbalanced translocations, or ring chromosome 22, leading to the loss of sections of chromosome 22, where the *SHANK3* gene is located, or by loss of function variants of *SHANK3*. A total of 3,100 PMS cases have been identified worldwide by the PMSF to date, with an estimated prevalence of about one in 1/8,000 – 15,000.<sup>2</sup>

PMS has a very wide and heterogenous constellation of symptoms.<sup>3</sup> Most individuals living with PMS are moderately to severely affected by language deficits and motor delays, autism or autism spectrum disorder (ASD), hypotonia, gastrointestinal dysfunction (most commonly constipation), and gait abnormalities. While scientific literature reports that a quarter of patients experience regression and loss of skills, this is likely to be much more common. Children with PMS are known to have pronounced hypo-reactivity including a high pain threshold, and only a quarter are effectively toilet trained. About a quarter of patients have epilepsy, including some with severe and potentially treatment refractory epilepsy. Sleep disturbances are a common PMS characteristic. Neuropsychiatric symptoms including bipolar disorder, catatonia, psychosis and schizophrenia are being increasingly recognized. Although all individuals have dysmorphic features, the nature and variability of dysmorphisms is non-specific.

The diagnosis of PMS is complex and is based on a detailed molecular analysis. A chromosomal microarray typically shows a terminal 22q13 deletion, and additional sequencing methods are used to identify sequence variants, although not all *SHANK3* variants cause PMS. Recent evidence demonstrates genotype-phenotype correlations.<sup>4</sup> Those with sequence variants and Class I deletions (including *SHANK3* only or *SHANK3* with *ARSA* and/or *ACR* and *RABL2B*) have fewer delayed developmental milestones, a higher cognitive ability, but more skill regressions and are more likely to have psychiatric diagnoses than those with Class II deletions (larger deletions). Those with Class II deletions were more likely to have a variety of medical comorbidities.

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<sup>1</sup> This clinical overview was adapted from the presentation delivered by Alex Kolevzon MD, at the November 8, 2022 PMS EL-PFDD meeting. Dr. Kolevzon is from the Seaver Autism Center, and a Professor of Psychiatry and Pediatrics at the Icahn School of Medicine at Mount Sinai in New York City.

<sup>2</sup> [www.pmsf.org](http://www.pmsf.org); Leblond CS, Nava C, Polge A, et al: Meta-analysis of SHANK Mutations in Autism Spectrum Disorders: a gradient of severity in cognitive impairments. PLoS Genet 10:e1004580, 2014

<sup>3</sup> Signs and symptoms of PMS reported in the literature and mentioned in social media are included in a Conceptual Model (<https://www.cureshank.org/pms-conceptual-model>).

<sup>4</sup> Levy T, Foss-Feig JH, Betancur C, et al: *Strong evidence for genotype-phenotype correlations in Phelan-McDermid syndrome: results from the developmental synaptopathies consortium*. Human Molecular Genetics 31:625-637, 2021

A wide range of potential PMS therapeutic approaches are being explored. Clinical trials include insulin-like growth factor 1 (IGF-1)-related therapeutic approaches, lithium and inhibition of pathways that regulate neuronal survival and synaptic plasticity. Intravenous immune globulin (IVIG), microbiome-related treatments, zinc supplementation, histone deacetylase (HDAC) inhibition, mGlu5 modulators, and endocannabinoid system modulation have been suggested as possible approaches for exploration. Gene therapy approaches to deliver the *SHANK3* gene into the brain and RNA therapies are also being developed and could potentially be disease-modifying.

### Meeting summary

The Phelan-McDermid Syndrome Externally-Led Patient Focused Drug Development (EL-PFDD) meeting was held virtually on November 8, 2022. This meeting represented an important opportunity for CureSHANK and PMSF to share patient and family perspectives on the challenges and unmet treatment needs of those living with PMS. The PMS EL-PFDD meeting was co-moderated by Geraldine Bliss, the co-founder and president of CureSHANK, and by James Valentine, JD, MHS, of Hyman, Phelps and McNamara.

Geraldine Bliss opened the meeting by welcoming and thanking all meeting attendees for their participation, including the FDA, industry sponsors, researchers and physicians around the globe. She provided an overview of PMS and described some of the many challenges faced by PMS families. She invited her fellow community of PMS families to call or write in during the program and to participate in remote polling, in order to have as many different PMS perspectives represented as possible.

**Dr. Wilson Bryan**, Director of the Office of Tissues and Advanced Therapy in the Center for Biologics Evaluation and Research (CBER) offered some opening remarks on behalf of the FDA. He described the purpose of the meeting, which was to help the FDA to think about how PMS clinical trials should be designed, what endpoints are meaningful to those living with PMS, and how to balance benefits and risks of a new treatment. He emphasized the importance of hearing the voice of the PMS community as well as individual voices discussing the full range of challenges. **Dr. Alex Kolevzon**, Professor of Psychiatry and Pediatrics, at the Icahn School of Medicine at Mount Sinai in New York City, provided the scientific review of PMS which served as a clinical foundation for the rest of the meeting. **James Valentine** provided an overview of the meeting structure and encouraged families and caregivers of individuals living with PMS to contribute to the dialogue via online polling, calling in by phone, and contributing written comments using the online portal.

Online polling was used to determine the meeting attendee demographics, shown in **Appendix 1**. Almost two-thirds of meeting participants represented individuals living with a PMS deletion subtype, a third of meeting participants represented individuals living with a *SHANK3* variant, and 3% were unsure about their loved one's PMS subtype.

Almost half of poll respondents were located in the US Eastern time zone, followed by equal numbers of poll respondents from Europe/UK, the US Pacific time zone and the US Central time zone. There were small percentages of respondents from the US Mountain time zone and from



Canada. The group was nearly evenly split by gender, with 52% of people living with PMS represented at the meeting female and 48% male. The largest age group represented at the meeting were children aged 5-10 years old, followed by individuals aged 11-20 years, adults aged 21-40 years, and children aged 1-4 years, and adults aged 40-60 years. None of the individuals living with PMS represented at the meeting were under 12 months or over 60 years of age. Individuals living with PMS were diagnosed across the age spectrum from 0-6 months up to 40 years. Most PMS diagnoses were made between 13 months and 5 years of age.

The meeting was attended by 399 people, including 9 individuals living with PMS and 306 parents, family members, friends and caregivers. The meeting was attended by 17 government representatives including those from the FDA and the National Institutes of Health. There were 28 scientists, 22 industry representatives, eight representatives from non-profit entities and six health care providers and several Scientific Advisory Board members, interested parties and consultants.

The PMS EL-PFDD meeting was structured around two key topics. The morning session was structured around Topic 1: *Living with Phelan-McDermid Syndrome: Symptoms and Daily Impacts*, and the afternoon session addressed Topic 2: *PMS Current and Future treatments*. The meeting agenda is in **Appendix 2**, and the questions provided for meeting discussion are in **Appendix 3**.

The morning session continued with five pre-recorded caregivers who were selected to represent a range of experiences of families living with PMS. James Valentine moderated a discussion between several people who served on a live Zoom panel as well as people who dialed in by phone. Additional relevant comments entered through an online submission form were read by Geraldine Bliss. The names of panelists and callers are listed in **Appendix 4**. As a reflection of the severity of PMS, not one of the panelists, speakers or callers were individuals living with PMS, but were caregivers and family members speaking on their behalf.

The afternoon session opened with a pre-recorded panel of five caregivers who described different medical therapies and other treatments they use to address seizures and other disease manifestations. Again, meeting attendees participated in online polling, called in and submitted written comments which were added to the moderated discussion by James Valentine and Geraldine Bliss. Near the end of the meeting, **Larry Bauer** provided a reflective summary of the key messages he had heard throughout the meeting. **Kate Still**, PhD, Scientific Director of the PMSF, closed the meeting and described the next steps. She emphasized how proud she was of all the presenters and thanked them for their attendance.

The online polling results from Topics 1 and 2 are included in **Appendices 5** and **6**, respectively. To include as many voices as possible, an online comment submission portal was open for four weeks after the meeting. Selected comments are included in the body of this *Voice of the Patient* report, and all submitted comments are included in a separate document.

This *Voice of the Patient* report is provided to all PMS stakeholders including the US FDA, other government agencies, regulatory authorities, medical products developers, academics,

clinicians, and any other interested individuals. The final report, a video of the meeting and the accompanying document containing the submitted comments is available on CureSHANK's website at [cureshank.org](http://cureshank.org). PMSF will also post a copy of the report to [pmsf.org](http://pmsf.org). According to YouTube statistics, the meeting was streamed over 1442 times as of March 18, 2023.

## TOPIC 1: Living with PMS: Symptoms and Daily Impacts

During the first session, parents and caregivers shared their perspectives and experiences of living with PMS. They used online polling to select all the PMS-related health concerns that their loved ones experienced, they chose the top three most troublesome, they described the impacts that PMS had on activities of daily living and shared their worries for the future.

Parents shared stories about meandering diagnostic journeys and how it often took a great deal of time and effort before their concerns about developmental regression were acknowledged. Many individuals living with PMS have received multiple different diagnoses, including autism spectrum disorder (ASD). Some individuals didn't receive a PMS diagnosis until adulthood, which left parents asking themselves, *"What if my child was diagnosed sooner?"*.

The following section is organized by the results of the online polls and illustrated with parent and caregiver quotes.

The most impactful PMS-related health concerns include regressions, developmental delay, communication issues and muscle weakness.

Parents and caregivers used online polling to first select all the PMS-related health concerns that their loved one had and then to indicate which three were the most troublesome. Poll results are described below and in **Appendix 5, Q 1 & Q2**. Most individuals living with PMS experience many symptoms and each caregiver selected an average of seven. One thing that was very clear from the meeting was that **individuals living with PMS often have a complex and interrelated constellation of symptoms**.

*"Hudson has many other diagnoses in addition to Phelan-McDermid Syndrome, including intellectual disability with her IQ being 0.1%, feeding difficulty, hypotonia, ADHD, processing and motor planning delays and autism. Every year it seems like the gaps and deficits get bigger and wider and Hudson falls farther from where she should be developmentally."*- Amanda, mother of a seven-year-old daughter living with PMS (Class I deletion)

### Regression

While only a third of poll respondents said that their loved one had experienced regression and selected as a most troublesome symptom for only 19%, **regression is one of the most impactful characteristics of this disease**. Parents of younger children described how regression led to the loss of conversant speech and the parents of older patients described regressive neuropsychiatric episodes.

*“The toughest part of this diagnosis for us has been experiencing regression.” – Abby, mother of a six-year-old son living with PMS*

*“Just before his PMS diagnosis, Asa suffered a regression. Words he seemed on the grasp of speaking were no more, never to return. Sounds of progress were silenced. Asa remains nonverbal. We could no longer hope Asa had a mild form of autism.” - Arturo, father of a seven-year-old son living with PMS (SHANK3 variant)*

*“At the age of five, around kindergarten, was probably our best year. He had about 10 words. He was semi potty trained. He actually wore underwear, and it was a good time for us. We thought we were getting somewhere. And then the very little that he did gain, he lost.” - Martha, mother of a nine-year-old son living with PMS*

Chris described the changes after her son’s regression. *“This was a child who, prior to this, was going to the YMCA, swimming, laughing, enjoying being with others. ... He was looking to get a little job at a pet store. He loved going to the library, grocery store, socializing with friends, listening to music. He enjoyed getting dressed every day, taking a bath, brushing his teeth. Now, it's a celebration when we can get him to leave the house to visit his sister and his brother-in-law who he absolutely adores. ...Taking walks safely around the neighborhood. It takes two of us. We can't go one on one with him because he is a flight risk. And he's so strong now that he's a 22-year-old man who doesn't understand safety.” - Chris, mother of a 22-year-old son living with PMS*

*“Mary needs total care now. At one time she could feed herself, dress herself, bath herself including running her own bath water, swim with Special Olympics, volunteer at the library, work at Wendy’s, work at a sheltered workshop, participate in ARC activities, etc. Now she can do none of these things. She wept and became depressed as her abilities eroded away.” - Shelby, mother of a 49-year-old daughter living with PMS, diagnosed at the age of 42*

### **Developmental Delay/intellectual impairment (lack of safety awareness)**

This health concern was experienced by almost all individuals living with PMS and was ranked as the most troublesome health concern in the online polls because the consequences were so severe. Individuals living with PMS are unaware of risks and have a lack of safety awareness and often put themselves in danger, because they simply don’t understand the consequences of their actions on themselves or others. During the meeting and in comments, caregivers described many examples of dangerous situations and injuries sustained.

*“Not understanding concepts such as what a birthday is, what his age is, who his parents are is one thing. Not understanding what a hot stove or a hot anything is, what a danger a speeding car poses, is quite another and obviously a huge safety hazard. ... He is at high risk for elopement and if unhindered, he is at great risk of harm.” - Arturo, father of a seven-year-old son living with PMS (SHANK3 variant)*

*“She often puts herself in very unsafe situations because she is unaware of the danger or risk. She has fallen down a full flight of stairs, runs into walls and bruises without saying a word, slammed her finger in the car door and the list goes on.” - Amanda, mother of a seven-year-old daughter living with PMS (Class I deletion)*

Parents described elopement, which happens when an individual who is incapable of adequately protecting themselves, flees their safe environment unsupervised and undetected.

*“When he was only six years old, Bennett eloped. He ran down the street barefoot and without his helmet or his leg braces. A concerned neighbor saw him running in front of cars and pulled him out of the street. At that same moment, a police officer took over and asked Bennett his name, but he was unable to respond as he's nonverbal. They asked where he lived and again, only babbling was the response. The officer flashed his lights and turned on the sirens and Bennett was placed into the back of the police car, terrified. He was hitting himself, rocking back and forth, and the officer was very apologetic and I was just thankful my son was safe. When we got home, and in less than two hours, he tried to elope again.”- Avis, mother of an eight-year-old son living with PMS*

Some inadvertently injured themselves and other family members.

*“If I could define my son, I tend to say that he's something I like to call “dangerously mobile. ...There's no one in this world that loves my son as much as me. And there's no one in this world that gets hurt by my son as much as me. He kicks me, he punches me, he bites me. ... Never out of anger, purely because he doesn't understand what he's doing.” - Joanna, mother of a six-and-a-half-year-old son living with PMS*

*“She has almost managed to flip over the baby in his stroller and bouncy seat... as well as scooch under his swing while he was being rocked. She adores him and is never malicious... just curious and affectionately aggressive and thus is a constant threat to his well being and her own safety.” -Sarah, mother of a daughter living with PMS*

### **Communication issues**

Individuals living with PMS display a wide range of communication abilities. Some can communicate verbally, or with a device or show their parents what they want, while others have no receptive language and can't even understand what their parents say to them. Paired with intellectual disability, communication issues mean that some children can't articulate their most basic needs or even signal that they are in pain.

Mila was expressive and had over 300 vocal approximations before her regression.  
*“Now at age 11 we still don't have the skills that she had when she was two and a half.  
...Mila communicates by pulling us around the house, pulling our arm, and maybe using*

*our arm to lift up and point to something that is high. And that's for very basic wants and needs.” - Cyra, mother of an 11-year-old daughter living with PMS*

*Mike described his son as, “‘Non-verbal’ because he is quite communicative but he does not use words. He tends to perseverate around a few buttons on his communication device, so understanding his wants and needs, especially when not feeling well, is a challenge.” - Mike, father of a 21-year-old son living with PMS (Class II deletion, 7.74 mega bp)*

*“Asa's most disabling feature is his almost non-existent receptive language, as if he wakes up every morning in a country where he doesn't understand the language, he appears to understand fewer than 20 words and less than half of that without visual context clues, and the words he does understand are all because of very repetitive work and therapy to learn them.” - Arturo, father of a seven-year-old son living with PMS (SHANK3 variant)*

*“And I think that people take for granted that communication sometimes is just the issue, but it goes a layer further in our family that my son doesn't even understand his wants or needs. So how can someone have the desire to even truly communicate when they don't even know what they want?” - Joanna, mother of a six-and-a-half-year-old son living with PMS*

### **Challenging behaviors, (repetitive, self-injurious)**

Many of the challenging behaviors described intersect with both intellectual impairment and psychiatric problems. Some behaviors are the result of sensory issues. Some described self-harm, and behaviors that put themselves and other in danger.

*“Last year, massive anxiety blew up into intense self-injurious behaviors, specifically in the form of punching himself in the face, giving himself black eyes and hitting his head against walls, doors and floors. ... At its worst, he tried to hurt himself hundreds of times per day, often triggered by being anywhere except in his own bed, watching his favorite movie and eating his favorite snacks.” - Arturo, father of a seven-year-old son living with PMS (SHANK3 variant)*

*“He is non-verbal and we wonder if he sometimes gets frustrated that he cannot communicate effectively. In these cases, he will bite himself and has permanent bruises on his hands from biting.” - Frances, mother of a five-year-old son living with PMS*

Laura’s son was always very gentle and non-aggressive. *“We suddenly had this huge flip in his personality where he was destructive, just grabbing people, pulling hair. I mean, he doesn't really understand that he's hurting people, so it's not so intentional. ... If he's sitting behind you in the car, he'd wrap his arm around your throat when you were driving. It was incredibly dangerous for everyone in the family and him. ...He would just*

*start throwing furniture at people. We went through five computers, iPads galore in a two-year period.” - Laura, mother of a 22-year-old son living with PMS*

*“Worst days: perseverating on the word "door" shouting it for hours, only sleeps for a few hours at night (at most), slamming doors, breaking objects, aggression, runs out of house nude to take out trash, unfocused and impulsive.” - Denise K., parent of a 40-year-old son living with PMS*

Some families have had to change their lives to avoid triggers.

Chris is monitoring all aspects of her son’s life looking for patterns and triggers. *“Being able to listen to music and even having a television in our house is a celebration ... because, for whatever reason, it can be such a trigger for him.” - Chris (caller), mother of a 22-year-old son living with PMS*

Some individuals living with PMS try to comfort themselves with “stimming” (self-stimulating) behaviors that include repetitive body movements, such as rocking back and forth or finger-flicking.

*“My daughter Ellie does not play with toys. ...Her version of play is stimming. She will stim on this lamp for hours and her newest thing is to go through our house stimming on doorknobs.” - Hope, mother of a six-year-old daughter living with PMS.*

*“Josh has a lot of sensory issues. When he gets more sensory input (for example in the summer when he can be outside more), he’s calmer, sleeps better and is generally happier. At other times, when he doesn’t have the right sensory input, he gets super “stimmy” and more in his own world.” - Albert and Valentina, parents of an eight-year-old son living with PMS*

Some individuals living with PMS have oral sensory issues and try to put everything in their mouth. Others have pica and eat inappropriate objects.

*“He always needs a chewy as he will pick up non-food items and chew on them and is very oral sensory fixated.” - Angie, mother of a 13-year-old son living with PMS (Class I deletion)*

*“He mouths a LOT. He will chew on his iPad case while watching TV. He will also rip up books and put the paper in his mouth. He won’t typically swallow it but he will chew on it often. The other day, he put an entire ball of play doh in his mouth.” - Albert and Valentina, parents of an eight-year-old son living with PMS*

*“She will reach up and pull out ponytails and chew and attempt to eat her own hair if bored. She’s been known to remove headbands, clippies, and especially face masks during the pandemic and stuff them entirely into her mouth. I am constantly panicked*

*that she will choke on something. Due to her cognitive impairment and lack of gross motor skills, she is not able to determine what is safe to chew and how to get something unsafe out of her mouth if she does start to choke.” -Sarah, mother of a daughter living with PMS*

*“He will put everything in his mouth and as a result has had multiple surgeries to remove foreign objects. His pica is extremely dangerous and requires near constant supervision to keep him safe. Currently, we are looking for a residential placement for our son and the primary reason for group homes to reject his placement is his pica.” - Shelley T., mother of a 20-year-old son living with PMS*

*“Alexander suffers from Pica as he constantly needs oral stimulation. He will put his hands in his mouth, mouth anything in sight including the inside of my car door, the corners of the walls, and furniture.” - Jessica, mother of a 14-year-old son living with PMS*

One of the more challenging PMS behaviors is fecophilia, where individuals develop a strong interest in fecal matter. Many described how their children will put their hands into their soiled diapers and try to smear the feces on themselves or their surroundings.

*“She has on a number of occasions reached into her diaper and created a mixed media wearable, edible art project. While we are proud of her creativity, we really don't enjoy cleaning brown off of All. The. Things.” - Sarah, mother of a daughter living with PMS*

*“She has to wear onesies and have a caregiver so she doesn't get her hands there to eat and smear feces everywhere.” - Karen D., grandmother of a five-year-old girl living with PMS*

### **Muscle weakness (hypotonia, motor planning difficulties, abnormal gait)**

Most individuals living with PMS experience muscle weakness, including motor planning difficulties, abnormal gait and hypotonia. Some described how their newborn children felt “floppy” and how hypotonia led to hypoxia resulting in time in the ICU. Fine motor skills can be absent, and some have little control of their limbs. A lack of spatial awareness and poor balance puts them at risk of falls.

*“She is unable to sustain weight-bearing positions in both upper and lower extremities and has difficulty sustaining any anti-gravity positions. She has poor body awareness, poor proprioception, and no safety awareness. In standing and transitioning, she has no righting reaction or protective extensions to catch herself or recover from loss of balance. She demonstrates a quick immediate loss of balance with complete collapse to the floor, making therapy and daily life dangerous and difficult.” - Lacy, mother of a nine-year-old daughter living with PMS (Class II deletion)*

*“Sammi started walking when she was two, so her low muscle tone might not be severe, but her body coordination is not so great. She's still learning to use her hand to protect her face when she falls.”* - Shiori, mother of a seven-year-old daughter living with PMS (Class II deletion)

*“They may want to play with toys but because their fine motor skills are so bad, they can't, and that's frustrating.”* - Ryan, father of a 13-year-old son living with PMS (terminal deletion, including all of the SHANK3 gene)

*“As my son has gotten older, we have seen a decline in walking due to drop foot, frequent bouts of myoclonus dystonia, tremor, and many Parkinson's-like symptoms. As he is very active, the difficulty with walking and movement impacts his ability to do the things he enjoys, like hiking and swimming.”* - Laura, mother of a 22-year-old son living with PMS

### **Psychiatric problems (anxiety, bipolar, psychosis, catatonia)**

Psychiatric problems are often severe, and many parents described how their loved one experienced a range of symptoms including anxiety, depression, bipolar disorder, OCD, delusions and paranoia.

*“For us mostly it was anxiety and depression. She would just cry at nothing, or she wouldn't be able to understand what you were talking about, confusion would set in, and then that would lead to anxiety with her.”* - Cynthia, mother of a 19-year-old daughter living with PMS

Tesi's daughter developed a severe bipolar disorder at the age of 14. *“First came weeks of sleepless nights, talking loud and fast, alternately sobbing or roaring with laughter. She had paranoid delusions. ...This manic state was followed by months of a deep depression, during which we had to feed her and dress her and toilet her. ... At age 16, severe OCD hit overnight. She was afraid that something bad would happen to our cat. For three solid months, she followed the cat from room to room, watched the cat sleep and asked constantly whether the cat was okay. She couldn't bring herself to play or eat, and she was terrified to leave the house.”* - Tesi, mother of a 22-year-old daughter living with PMS (SHANK3 variant)

Sometimes their children were frozen in a catatonic state, fearful and unable to respond.

*“Catatonia is a recent diagnosis. ...Matthew suddenly stopped walking unassisted, frozen unless he was holding onto you. He had never seemed fearful before and suddenly he would not walk a few steps in the house without holding on. ... Over the next two years, he had several month-long periods where he was lethargic, losing over 10 pounds each time and generally failing to thrive. ...This particular affliction has been devastating as Matthews no longer himself when the catatonia strikes”* - Mike, father of a 21-year-old son living with PMS (Class II deletion, 7.74 mega bp)



Other times they are manic, moving constantly and unable to engage.

*“In high school, his world changed dramatically. He became manic OCD. He literally did not sleep for days. He was destructive, aggressive, and he was scared and there was nothing we could do to help him, despite everything we were trying. He was hallucinating, he experienced catatonia, both the stuporous and hypermotoric versions. ... On the days when he's not well and not himself, he may be pacing purposelessly, as if he cannot stop moving and he has no control. It almost looks painful. He cannot engage in anything, so he's just moving constantly. At times, he looks as though he's drowning, but he is not in water. He will flail about as if he's looking for some help because he cannot control what's happening to his body or his brain.”* - Chris, mother of a 22-year-old son living with PMS

Psychiatric incidents were often associated with subsequent regression.

*“I spoke with over a hundred families of teens and adults with Phelan-McDermid who had severe psychiatric illness. I learned how common this complication is and how very unusual our children's responses to psychiatric medications often are. I also learned that regression can hit after the psychiatric illness, stealing language, motor skills, continence and self-awareness, a terrible possibility that hangs over our families.”* - Tesi, mother of a 22-year-old daughter living with PMS (SHANK3 variant)

*“Mary's life dramatically changed at age 29 when she had a neuropsychiatric regression from which she never recovered. Currently, she has a dementia type presentation with Parkinsonism, dystonia and chorea, speech comes and goes.”* – Shelby, mother of a 49-year-old daughter living with PMS

Many are hospitalized for extended periods or even institutionalized.

*“My son has had intense and very severe psychiatric symptoms. As a result, he is institutionalized, and my other children have been impacted significantly. We didn't know that his diagnosis was PMS until he was older and once catatonia and psychiatric symptoms robbed us of our son and his skills. ... On his worst days, he is manic, refuses to sleep, chokes on his food, has toileting accidents, and is aggressive to others.”* - Laraleigh, mother of an adult son living with PMS

### **Sleep difficulties**

Sleep difficulties impact the entire family and often exacerbate seizures and psychiatric issues.

*“Having her staying asleep throughout the night, having her being able to sleep eight hours straight without waking up, for us, that's rare. Being able to have full sleep, that's absolutely rare.”* - Carla F., mother of a four-year-old daughter living with PMS.

*“The neurologist told us lack of sleep can cause seizures. She is shallow sleeper. She wakes up middle of night with smallest noise.”* - Shiori, mother of a seven-year-old daughter living with PMS (Class II deletion)

Sleep issues can result in anxiety and depression. *“We had to put a video camera on her at night ... and during this, we realized she was tossing and turning 70 to 100 times at night. So literally she wasn't sleeping.”* - Cynthia, mother of a 19-year-old daughter living with PMS

*“We think that the lack of sleep contributes to the manic behavior. She doesn't sleep well. That could be the manic. The bipolar could be something else that's going on so that sleeplessness contributes to it.”* - Michael, father of a 38-year-old daughter living with PMS, diagnosed only one year previously

*“Laney can wake anywhere from 1-10 or more times a night and waking up between 4 and 5 am is normal. Sleep exhaustion and disturbance has made it very hard for us to carry on a normal life as a family. We lack energy and patience to take on normal daily activities, let alone the extra and fun activities that typical families get to experience.”* Katie, mother of a six-year-old-daughter living with PMS

### **Bowel or bladder issues (constipation, difficulty urinating, neurogenic bladder)**

Many children with PMS need to wear diapers, either because they are not toilet-trained or are unable to articulate when they need to use the bathroom. Some children experience retention and bladder spasms, which leads to accidents. For others, constipation can be extreme. This symptom can be complicated by challenging behaviors including sensory disorders and fecophilia.

*“Urinary retention and bladder spasms is a big problem now, too. Holding in, not controlling his bladder, urinating through his diaper at school and having to change clothes.”* - Ryan, father of a 13-year-old son living with PMS (terminal deletion, including all of the SHANK3 gene)

*“We didn't realize that our daughter had a problem until we went to see a urologist for urinary purposes, and they did a scan of the rectum at the time, and her rectum was four times larger than a normal rectum should be. At that point in time, we didn't even know that she had a problem with GI.”* - Cynthia, mother of a 19-year-old daughter living with PMS

*“He needs a one-to-one aid at school to help with his daily routine, change his diapers, he is not bowel movement-trained due to his constipation. It is always unpredictable when he needs to have a BM as he doesn't tell us, and he does it standing up in his diaper.”*- Angie, mother of a 13-year-old son living with PMS (Class I deletion)

*“She definitely has GI issues where she can suffer from extreme constipation and we can notice that a little bit by her pushing on her stomach. But that's after [many] days.” - Cyra, mother of an 11-year-old daughter living with PMS*

*“Sensory issues get in the way of training. She cannot control the urge to touch, smell and taste her poop. Therefore, she is in pullups. My concern is the selection of pull ups as she gets older. Also, adult sized changing tables or changing tables for vehicles are basically nonexistent. I time our outings based on her poop schedule.” - Tanya, mother of a daughter living with PMS*

### **Feeding difficulties**

Feeding difficulties include difficulties with swallowing, choking, reflux, cyclical vomiting, and rumination. Some individuals living with PMS require gastric tubes to ensure that their children had enough nutrition to survive.

*GI issues can emerge in infancy. “He had acid reflux since he was a baby until age eight. Eventually, the acid reflux became cyclical vomiting from age three to eight when he would regurgitate his food about 40 times a day uncontrollably. ... We were in and out of the hospital from age three through eight due to dehydration and failure to thrive because he lost 10% of his body weight. ... It was almost like a hiccup of vomit every few minutes.” - Angie, mother of a 13-year-old son living with PMS (Class I deletion)*

*“Reflux is one of his main issues, and we haven't found a med that controls that. ...He smells like vomit all the time.” - Megan, mother of a one-and-a-half-year-old son diagnosed when he was four weeks old*

*Amanda has had to administer the Heimlich maneuver many times when her daughter has choked. “Because of Hudson's motor planning, delays, hypotonia and intellectual disability, she can't identify appropriate bite sizes, doesn't have the mouth and jaw muscles to chew her food and often continues to put food in her mouth without realizing she never swallowed her last bite.” - Amanda, mother of a seven-year-old daughter living with PMS (Class I deletion)*

*“My son used to love food, he could feed himself, but like many of the other callers and parents have said, he would shove food in his mouth. ... And then all of a sudden with the regression, he stopped eating, he started choking, he started throwing up daily. ...We saw a GI specialist and eventually he got a feeding tube. ... This was really hard to watch for a kid that just loved food.” - Heidi, mother of an adult son living with PMS*

*“Rumination syndrome is the unintentional and consistent regurgitation and bringing up of undigested food from the stomach and re-chewing it. ...The rumination's a big thing for us right now. ...He does it hundreds of times a day.... Every time he eats, he does it.” Ryan explained that rumination syndrome is a sensory issue, “I think he doesn't want it in his mouth, so he's pulling it out of his mouth and it's getting everywhere. ... We just*

*get concerned over the longevity of things coming up and down his esophagus. Well, what kind of damage will this do to him? How is it affecting his quality of life? Being that he doesn't talk, we really don't know. Doctors are telling us that there's nothing you can do, there's no current cure.” - Ryan, father of a 13-year-old son living with PMS (terminal deletion, including all of the SHANK3 gene)*

## Seizures

Parents described a wide range of seizures including abnormal neurological behavior that doesn't quite fall into seizure behavior as well Lennox-Gastaut syndrome (LGS), a type of medically-refractory epilepsy. Seizure triggers can often be unexpected, and seizures often lead to regression. Parents discussed their fear of sudden unexpected death in epilepsy (SUDEP), which is a real threat for individuals living with PMS.

*“Seizures for Lily act like ‘cleaning the chalk board’ of the brain and skills such as eating, talking or even walking and start all over is depressing.” - Laura, mother of a daughter living with PMS*

One episode of a TV show, *“Was causing her so much distress that she started having gelastic seizures. I did not even know that was a thing. They've considered her borderline for developing epilepsy for a while. They won't give us a full-blown [epilepsy] diagnosis because she's only had febrile and gelastic [seizures].” - Hope, mother of a six-year-old daughter living with PMS.*

*“Last year Gavin started having seizures. ...He started to lose the ability to feed himself, walk and several other new issues. ... Gavin continues to this day to have 500-1000 seizures a day and we have exhausted all medical means to stop them. This requires someone to be in his room 24/7 to tend to his medical needs.” - Carrie, mother a son with PMS*

Ethan's mom slept on his bed for months, trying to protect him from seizures and death. *“Most of his seizures were less than a minute long and they'd come around not needing intervention, maybe vomiting or being sleepy for the rest of the day, or they would come in clusters.” – Cathy, grandmother to a boy who died at the age of six from PMS (Class II deletion)*

## High pain tolerance

High pain tolerance is complicated by intellectual disability and communication issues, as individuals living with PMS may not sense how badly they are injured or may be unable to communicate to their caregivers if they are injured.

*“She's got this high threshold for pain like so many others with PMS. ... And there have been times where she comes home from school and she's got some injury and the teachers didn't realize that anything had happened until it was too late.” - Cyra, mother of an 11-year-old daughter living with PMS*

*“When our daughter was 14, she fractured the radial head of her elbow from falling off her adaptive adult trike. We didn’t even realize she was hurt until the next day because she was holding her elbow at an odd angle. She never cried or acted like she was hurt.”* - Janet, mother of a daughter with PMS

### **Body temperature regulation**

Body temperature regulation is a challenge and overheating can sometimes lead to seizures.

*“Now he also has trouble controlling the body of his temperature with the catatonia and autonomic dysfunction.”* - Heidi, mother of an adult son living with PMS

*“She had difficulty regulating body temperature and then once it started, her fever raises quickly. Whenever she has a fever, it is followed by a seizure.”* - Shiori, mother of a seven-year-old daughter living with PMS (Class II deletion)

*“Her body can’t regulate on its own and she is at a huge risk for easily over heating in our hot California summers.”* - Amanda, mother of a daughter living with PMS

### **Other symptoms not mentioned in the polls**

Parents and caregivers of individuals living with PMS mentioned a large number of additional symptoms.

- abdominal migraines
- breathing difficulties and asthma
- congenital heart defects including total anomalous pulmonary venous return and atrial septal defects
- CNS malformations/growths - arachnoid cyst near the cerebellum, glioma and schwannoma, hypoplasia of corpus callosum,
- dystonia and muscle spasms
- dysmorphisms including scoliosis, cleft lips and palates, pronating feet and varus ankles,
- growth hormone deficiency, short stature
- hip dysplasia and hip dislocation
- hypothyroidism
- immunodeficiencies/repeated infections
- inflammation
- inner ear problems
- Kidneys – malformations and chronic kidney disease
- limbic encephalopathy
- lymphedema/cellulitis
- mitochondrial disorders
- osteopenia/osteoporosis
- pain, despite high pain resistance
- PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection)
- tall stature
- visual disturbances including nystagmus, cortical visual impairment

Caregivers also described the large number of injuries and multiple hospitalizations that their children with PMS had endured.

*"[Our son] has been admitted to the ICU over five times thus far in his life, mostly for breathing issues and aspiration problems." - Avis, mother of an eight-year-old son living with PMS*

*"She was recently diagnosed with osteopenia, following two leg fractures in two years. The first fracture was treated with a typical cast for two and a half weeks, resulting in a pressure wound, requiring wound care for nine weeks. The second fracture was treated with a knee immobilizer, as the temporary splint left another significant wound." - Lacy, mother of a nine-year-old daughter living with PMS (Class II deletion)*

*"My son has Lennox-Gastaut syndrome, a type of medically-refractory epilepsy. At the age of 24, he continues to have 300+ seizures per month. Combined with impulsiveness and a tendency to elope, he is at extremely high risk of injury, which has resulted in countless trips to the ER." - Brad, father of a 24-year-old son living with PMS and LGS (Class I deletion)*

PMS has severe quality of life impacts for those living with the disease, as well as on parents and siblings.

Parents and caregivers used online polling to indicate the top three activities of daily life that are important, but that their loved one is not able to do or struggles with, due to PMS. While poll results are described below and in **Appendix 5, Q3**, parents and caregivers emphasized that **all activities of daily life are impacted by PMS**. In the polls, self-care, communicating needs or wants and socializing with peers and siblings are the most important activities of daily life impacted by PMS selected in the polls. Many PMS impacts including injuries, challenging behaviors and property damage were described in the previous section of the report.

*"Phelan-McDermid syndrome has robbed my daughter of so many things every other neurotypical child experiences. She may never drive a car. She may never be able to be alone or have a moment of privacy. She might never have any real friends. There are so many, 'she may nevers'." - Amanda, mother of a seven-year-old daughter living with PMS (Class I deletion)*

### **Family life and family relationships are profoundly impacted**

Although the impacts of family life were not included as a poll option, they were discussed extensively throughout the meeting and in the online comments. Joanna described how they were a "family divided", which resonated with other PMS families and was repeated throughout the meeting by other caregivers.

*"I completely resonate with the "family divided in two" comment by the panelist. So much of the PMS manifestation we are facing has split our family in this way with one parent always needing to be able to stay home with one to provide her with a safe stable environment, while her siblings are active in the community, travel, etc." - Anna, mother of a daughter living with PMS*

*“The reality is, I ask my other child to give up so much because we have to stay home, or we have to leave the festival after we've only been there for an hour because her brother needs a new diaper, or there's just not the proper space for him. So, it's difficult because I know he doesn't understand what he's limiting the rest of the family with. But I understand, my husband understands, his sister understands.”* - Joanna, mother of a six-and-a-half-year-old son living with PMS

*“Being able to do anything as a family has always been difficult due to many issues, including sensory overstimulation in public places, sometime leading to tantrums or shut down, not understanding you cannot run out onto the soccer field of your brother's game (and having a tantrum when stopped), being able to sit down at a holiday dinner with family and have a conversation without interruption or "someone" wanting to leave immediately (still an issue at age 40), etc.”* - Denise K., parent of a 40-year-old son living with PMS

### **Self-care (bathing, dressing, toileting)**

Most parents and caregivers selected this as their top activity of daily life impacted by PMS, as most individuals living with the disease require 24-hour care and supervision, even during sleep. Many caregivers described how much effort it took to move, bathe and toilet their growing children, and many described how difficult it was to keep their children entertained all day.

*“Avenly is nine years old and weighs 52 pounds. Positioning her, moving her, lifting her and transferring her are already difficult tasks and will only get more difficult as she grows.”* - Lacy, mother of a nine-year-old daughter living with PMS (Class II deletion)

*“Due to her hypotonia and spasticity, she is extremely difficult to dress as she stims, chews her hands, stiffens limbs and joints, kicks, wiggles, tries to sit herself up or fling herself off of the changing table while we attempt to insert limbs into clothing. Dressing an octopus would be an easier task.”* - Sarah, mother of a daughter living with PMS

*“He needs a one-to-one aid at school to help with his daily routine, change his diapers, he is not bowel movement-trained due to his constipation. It is always unpredictable when he needs to have a BM as he doesn't tell us, and he does it standing up in his diaper.”*- Angie, mother of a 13-year-old son living with PMS (Class I deletion)

*“I have to employ two nannies to be able to even go to the toilet, because when Artemis is at home she needs help with everything, walking, entertaining, drinking, eating, toileting and communicating. She can do absolutely nothing by herself.”* - Penny, mother of a six-year-old daughter living with PMS (Class II deletion)

### **Communicating needs or wants**

Communicating needs or wants is an important activity of daily life impacted by PMS. Most individuals living with PMS are unable to communicate when something is wrong, when they

are ill, injured and when they are experiencing pain. This can be disastrous when combined with high pain tolerance. During the meeting parents described potentially disastrous encounters between their children and the police or the medical system.

*“At school, Hudson is very verbal, but she typically is just reciting and scripting what she's learned to say. She cannot actually communicate what she needs or advocate for herself if she needs help, is in danger or is hurt. Knowing your seven-year-old doesn't have a voice to speak up for herself in a school system that isn't set up for those with disabilities tears me apart.”* - Amanda, mother of a seven-year-old daughter living with PMS (Class I deletion)

*“Due to his communication challenges, it took years to diagnose his abdominal migraines and catatonia. He has repeatedly gone through battery of tests as we pursue various theories of what ails him, only to learn it was something else.”* - Mike, father of a 21-year-old son living with PMS (Class II deletion, 7.74 mega bp)

*“We are constantly having to guess what he wants, what hurts, what makes him happy, where does he want to go, does a medicine give him side effects, is someone not nice to him at school or on the bus, how did he get that bruise and on and on and on.”* - Amy, mother of a 17-year-old son living with PMS

*“We've had many hospitals take away his iPad because they don't allow them in psychiatric program, like phones and things, but he has no other way to speak but through his iPad.”* - Laura, mother of a 22-year-old son living with PMS

Without communication some parents don't know their child's preferences and don't have the relationship that they wished for with their child.

*“There are so many things we have no idea about and have never known. Her favorite color or what she might want for a birthday present or a Christmas present. I can come up with 15 things for my son, but I can't come up with one good one for my daughter.”* - Cyra, mother of an 11-year-old daughter living with PMS

*“We struggle daily with her inability to communicate with us, as she is non-verbal. ... The hardest part right now is not having access to my child- she doesn't seem to know we are there most of the time, she doesn't react when I walk into the room. We are invisible to her.”* - Kimberly, mother of a three-year-old daughter living with PMS

### **Socializing with peers/siblings**

Challenges socializing with peers and siblings is possibly one of the most heart wrenching impacts of living with PMS. Parents described how their children living with PMS were socially and emotionally isolated.

*“Her social, emotional and psychological development has been greatly impacted by not being able to do what her peers can do. She is unable to live life at eye level and interact*



*with others in an age-appropriate way. As a parent, it is heartbreaking to watch your child live this way.” - Lacy, mother of a nine-year-old daughter living with PMS (Class II deletion)*

*“He has a younger sister, London, who dreams of the day her brother can talk and play with her, but he has no interest in playing with other kids and can only communicate short sentences on his iPad talker augmentative alternative communication device.” - Angie, mother of a 13-year-old son living with PMS (Class I deletion)*

*“She cannot do anything that a typical 12-13-year-old can do. She has no friends, and cannot play with her cousins of the same age, or converse as they do.” - Ro, parent of a 13-year-old daughter living with PMS*

### **Participating in social engagements/events, travel and vacation**

Parents described the many barriers encountered when trying to participate in social engagements and events such as recitals, sporting events and church. Many of these barriers were similar to the ones faced when travelling or trying to vacation as a family. Low muscle tone means that children don't have the strength and coordination for sports or outdoor pursuits. Parents described loud and disruptive behaviors, accessibility and space challenges with wheelchairs and medical strollers, and their requirements for a private place to change and clean an adult child. Regression robs individuals living with PMS of their interest in activities.

*“I have a daughter that dances, and if Carter's being very vocal, we might exclude him from the competition and then you feel guilty for isolating him.” - Ryan, father of a 13-year-old son living with PMS (terminal deletion, including all of the SHANK3 gene)*

*“I want my family to be able to do these things together “. Carla wants her family to participate in normal activities like watching her oldest son's baseball tournament or attending church together. “I'm his mom, I want to watch him play. But Michael's coaching the team, so if I go to watch Joseph play, it means I have Matthew, the wheelchair, the service dog, the whole shebang, and my focus is really on Matthew, on making sure Matthew is content.” Attending church is also a challenge. “The Catholic mass is quick, an hour, but it's a lot to sit through with a child who is having the repetitive behaviors that are challenging, the screeching, the stimming, and just all of those different things. It makes it hard for us to even go to church as a family.” – Carla D., mother of a seven-year-old son living with PMS*

*“We live in beautiful California, we can't go for a hike as a family. We actually took our first family walk around the block just this past weekend because even though he's six and a half, my son has always struggled with walking because of his hypotonia. He's never had the strength or the focus to make it truly around the block.” Hypotonia also*

prevents her son from safely enjoying amusement park rides, even at accessible parks. - Joanna, mother of a six-and-a-half-year-old son living with PMS

*"In her adult years, Jo actually needed two people to 'access the community' because Jo could bolt off, push people randomly, sit on ground in dangerous places. Joanna's home always needed to be deadlocked to avoid her escaping. Jo could run! On her worst day, Jo would be aggressive, scream for long periods, climb tables, move furniture dangerously."* - Gail, mother of a daughter who passed away from PMS complications

*"Special Olympics and sports used to be the best part of Kimmy's life. Practicing, exercising, being a part of the team with her friends, getting to cheer them on during practices and games. She has no joy for these activities now, they have become buried somewhere in her mind."* - Karen, parent of a 22-year-old daughter living with PMS

*Sarah described how her daughter has a lot of "blow-outs" requiring full changes, bathing and cleaning. "This is a regular occurrence that causes great anxiety and difficulty trying to take her anywhere as there is no telling when and where she will relieve herself. She is so large she cannot fit on changing tables in any public restrooms, so we must do our best to find a safe, private floor space to lay her down and change her there."* - Sarah, mother of a daughter living with PMS

### **Attending school or having a job**

Throughout the meeting, parents and caregivers described the accommodations and extra staff required for their children to attend school. Many children are unable to attend school because of their psychiatric issues and challenging behaviors. Many absolutely rely on school-based supports and programs; a challenge is that they eventually "age-out" of the school system and supports for the remainder of their lives vary dramatically based on where they live.

*"This summer, Amadi turned 22, aged out of school and lost her teachers, her friends, and routines. In July, she slept less and less and in August, broke into full blown mania and psychosis...She began to believe that the people she misses so much are dead under rocks. ... With the help of her team, we got her back to herself and to reality, but she's fragile and we are sad and tired and worried."* - Tesi, mother of a 22-year-old daughter living with PMS (SHANK3 variant)

Many parents described how one parent had to leave their job to care for their PMS child.

*"As a result of Sam's PMS, I have given up my career to be his caregiver. I have given up all my interests and passions because they do not align with what Sam is able to do. I often share with others that living with PMS feels like a prison. We are kept away from the people and activities we love in order to care for our son and provide him the best possible life."* - Shelley T., mother of a 20-year-old son living with PMS

*“My husband had to leave employment to become his full-time caregiver. Prior to that, I was on leave from work to care for him.” - Chris, mother of a 22-year-old son living with PMS*

### **Routine medical/dental care**

Individuals living with PMS are unable to care for themselves, and their teeth often suffer. Simple things like dental cleaning require sedation. In addition, individuals living with PMS often damage their teeth when chewing on hard and inappropriate objects.

*“There is nothing wrong with my 7-year-old son's teeth, so far as we are aware, due to his SHANK3 variant PMS. However, we just recently had to get THIRTEEN cavities filled, narrowly missing a pulpotomy and crown. ..Due to his severe intellectual disability, he is entirely clueless about the point of keeping teeth clean or going to the dentist. We can \*kind of\* brush his teeth, but flossing is impossible, and dental cleanings will, going forward, require sedation because he is now too strong to hold down. Last time we tried, even with five adults and a papoose-like contraption, we could barely keep him still so the dentist could just examine his teeth. He just does not understand, and he is very strong.” - Talya, mother of a seven-year-old son living with PMS*

*“A big problem we are facing right now is dentistry. Everything from finding a special needs dentist to full IV sedation for a cleaning and X-rays is a real challenge”-Liz, mother of a son living with PMS*

### **Ability to eat by mouth**

Individuals living with PMS have challenges with eating. These can include challenges getting food to their mouths because of motor control issues, shoving even more food into their mouths when they are already full, insufficient chewing and choking.

*Amanda is traumatized from her daughter choking so frequently. “Just reliving the events of these near death situations is unbearable, all while knowing the next one could be just around the corner and hoping it's not the unthinkable.” Amanda described having to, “Spend so much time cutting up food into tiny pieces, stressing over what food is safe to send to school, standing right by her while she eats every single bite, reminding her to chew her food and wait before taking another bite.” - Amanda, mother of a seven-year-old daughter living with PMS (Class I deletion)*

*“She can feed herself bits of food on her tray and use her cup independently, but we have to monitor her constantly as she lacks motor control and will fling most of the contents off her tray or overstuff her mouth and choke on things. While she has enough dexterity to grab some finger foods and place them in her mouth, she seems to lack cognitive awareness that food is in front of her and has to be constantly reminded with hand over hand movements and verbal instruction to grab her food and put it in her mouth.” - Sarah, mother of a daughter living with PMS*

Parents and caregivers have many worries, especially for how their loved ones will be cared for in the future.

Parents selected three closely related worries as their top three worries about their loved ones' condition in the future: the worry that their loved ones will be completely dependent on caregivers; that their symptoms will get worse; and that they will be unable to communicate health problems. Poll results are described below and in **Appendix 5, Q4**. These worries all reflect parents' concerns about ensuring their loved ones' quality of life and the uncertainty about their ability to care for their children's needs in the future.

### **Complete dependence on caregivers**

The top worry for parents and caregivers was their loved one's complete dependence on caregivers, which was closely tied to their fear of being unable to care for their adult children, and finding them a place to live as their needs increased.

*Jenn described how physically demanding it is to care for her disabled daughter. "We have to physically pick her up and put her places. We have to care for her in every aspect: changing her pull up, giving her shower, brushing her teeth. And what does that look like when she's a grown adult? And how our own bodies going to be able to keep up with her and to give her the appropriate level of care? And then there's the other side of that is the financial side that she's seven, but we are already, for years have been already thinking about how are we going to support her for the rest of her life in a way that gives her dignity and comfort and safety. And those are big things to think about." - Jenn, mother of a seven-year-old daughter living with PMS*

*"I'm sitting here thinking about what happens if Matthew lives longer than me? Who's going to take care of him if my husband and I go first? And that's a terrifying thought of who would love him like we do? Who would do everything we do for him? In a lot of ways he is like a baby, he requires total care, total attention for his safety." - Carla D., mother of a seven-year-old son living with PMS*

*"There is nothing that terrifies me more than the moment I can't take care of my son anymore. And this is a conversation I know a lot of families have because we want to be there for our children forever." - Joanna, mother of a six-and-a-half-year-old son living with PMS*

*"Long term, I worry about the care and quality of life. While we are still able to care for our daughter in our home, we know we can control her care and monitor her caregivers. However, as she might need to live outside our home some point, it is very scary to think about needing to find a place to lovingly care for a child/adult with a low cognitive and intellectual functioning." - Anna, mother of a daughter living with PMS*

During the meeting and in comments, parents frequently mentioned how hard it was to find caregivers for their children outside of their family.

*“It's already hard to find good day programs and group homes for adults with developmental disabilities. When you add in bouts of psychiatric illness that require 24-hour availability of staff with mental health skills, it gets much harder.” - Tesi, mother of a 22-year-old daughter living with PMS (SHANK3 variant)*

*“We don't have caregivers outside of our immediate family because Avenly is so hard to physically manage safely.” - Lacy, mother of a nine-year-old daughter living with PMS (Class II deletion)*

### **That symptoms will get worse**

The second most selected worry was the worry that symptoms will get worse which is closely related to the fear of the unknown.

*“Something that I've heard PMS parents say time and again, and I agree with completely is the fear of the unknown of what the future holds. Our kids have such a gamut of outcomes and symptoms and we just don't know... and that's terrifying.” – Carla D., mother of a seven-year-old son living with PMS*

*We have no idea when this current [anti-anxiety] medication might stop working. It's terrifying to think about the future because without the development of treatments, we will almost certainly face ever greater challenges.” - Arturo, father of a seven-year-old son living with PMS (SHANK3 variant)*

*“One of the greatest challenges we face is the understanding that regression, seizures, psychiatric illness, among other challenges are always potentially looming, but there is no way to predict whether or when those challenges may present. We live with very cautious optimism every day knowing that overnight our world could change more than it already has.” - Stephanie, mother of a five-year-old son living with PMS*

### **Not being able to communicate health problems, including pain**

Many parents recounted stories of how their children had injuries that they weren't able to articulate. Others worried that their loved ones would not be able to communicate abuse.

*“We worry about the medications that he is on--that they will lose their effectiveness over time and cause other medical conditions especially those for which he would not even be able to tell us were an issue due to communication issues and high pain tolerance.” - Kristine, mother of a 22-year-old son living with PMS*

*“Right now she is little. She is with me or her therapists (ABA, OT, speech, PT) at all times. I'm terrified for the future when she goes to school or when she's an adult and relies on a caregiver. She can't tell them what she wants and she can't tell me if she's in trouble or if someone is mistreating her.” - Maureen, mother of a five-year-old daughter living with PMS*

### Other worries selected in the polls.

Parents and caregivers worried about limited social and recreational engagement, premature death, impacts on family relationships, uncontrolled seizures, uncontrolled pain and fear of falling or being injured. Many quotes reflected multiple fears.

Ryan fears that his son's social isolation may lead to mental health issues for himself and the rest of the family. *"I just don't want my child, as an adult, sitting in a room, bobbing his head back and forth and there's no quality of life for my wife and I or him. ...I'm thinking, what are we going to do to make Carter's life great when he is an adult, too? That's what I'm worried about in the future."* - Ryan, father of a 13-year-old son living with PMS (terminal deletion, including all of the SHANK3 gene)

Carla worries about her son dying first. *"What if he dies first? ...This isn't a normal thing for a mother to have to consider. I think so much of what's being discussed today by the panelists and the calls, these aren't normal things for families to have to deal with. And life with a PMS child is outside the realm of normal."* - Carla D., mother of a seven-year-old son living with PMS

Ethan's mom worried about seizures, even when he was having a seizure-free stretch. *"She worried that the longer the interval, potentially the longer the next seizure could be. On Sunday, March 20th, Ethan had been awake before 6:00 AM and he fell back to sleep for a bit. Dan checked on him and he too fell back to sleep on the couch. At 8:00 AM which is unusually late for Ethan, he was still quiet. Dan startled awake and found Ethan dead in his bed. He was six years old."* - Cathy, grandmother to a boy who died at the age of six from PMS (Class II deletion)

### Other worries not included in the polls

In addition to the many worries already listed, parents and caregivers worry worried about their children being harmed or harming others as a result of their behaviors. Some worried that their child would die before them.

*"One of my biggest worries stems from the fact that she has no fear. She has no concept of danger or boundaries with strangers. I worry in parking lots about elopement and am on high alert every time we leave the house."* - Emily, mother of a daughter living with PMS

Joanna worries that her son will hit a stranger. *"Staying awake so many nights terrified of what will happen when one day my son does this to the wrong person. ...I am terrified at the thought that my son will just hurt someone and they will hurt him back."* - Joanna, mother of a six-and-a-half-year-old son living with PMS

*"What does his future look like? How would that inability to communicate change his personality? Who will be able to care for him after we are gone? Will the next aspiration*

*be the one that gives him a pneumonia that he cannot recover from? Would it be better for him to go before us? Hard, dark, troubling thoughts to have about your child.” - Dottie, mother of a five-year-old son living with PMS*

## TOPIC 2: PMS Current and Future Treatments

Parents and caregivers used online polling to select all the different types of medications, medical treatments and therapies, non-medical and adaptive approaches as well as strategies that they had tried to help manage their loved ones PMS-related symptoms. They described how well these treatments worked as well as the various downsides. At the end of this session, parents indicated their preferences of the most meaningful changes that they would like to see from a future therapy for PMS.

Two themes not captured in the poll results came forward during the testimonies and discussion.

**Most parents are open to trying almost anything to try to relieve their child’s suffering; most have tried an incredibly high number of treatments and approaches.** Some described “the revolving door of medications”.

*“The amount of medication he takes is a lot because he takes medication for seizures, he takes medication for constipation, takes medication for reflux.” - Martha, mother of a nine-year-old son living with PMS and a neurotypical twin*

*“The medication revolving door is really difficult. ... We keep trying and then we try something else and then we try something else. And the difficulty not only with trying things all the time, different things. ... We try things again that we haven't tried for a year or two years.” - Sue, mother of a 28-year-old son living with PMS*

*“Our journey into treatments began early on before we even had the diagnosis. We tried an array of treatments, from pharmaceuticals to the holistic approach, including many drugs and therapies. ... We sought help from a neurologist, a chiropractor, and an OT.” - Lisett, mother of an 11-year-old son living with PMS (SHANK3 variant)*

**Some individuals were diagnosed too late to receive potentially beneficial treatments and therapies. Some received medications that caused more harm than good.**

*“But without that PMS diagnosis, [his catatonia] went unrecognized, was told that ‘it’s just’ behaviors. We were told lots of different things and we just kept trying therapies and meds and meds that actually probably caused him more harm.” - Heidi, mother of an adult son living with PMS*

Currently, there are no FDA approved treatments for PMS. Dietary or herbal over the counter (OTC) supplements, GI and sleep medications are the top approaches to address wide-ranging symptoms.

Parents and caregivers used online polling to select the many medications and medical treatments that their loved one used to manage PMS-related symptoms; each selected an average of three response options. Results are shown in **Appendix 6, Q2**. The top approaches dietary or herbal OTC supplements, GI and sleep medications, none of which were specifically developed or approved for PMS, and none of which have demonstrated efficacy for individuals with PMS.

### **Dietary or herbal over the counter (OTC) supplements, multivitamins**

Two-thirds of parents use dietary or herbal OTC supplements and multivitamins including, vitamin B7 (biotin), vitamin B complex, vitamins C, D, E, folic acid, calcium, zinc, Coenzyme Q10 (ubiquinol), levocarnitine, probiotics and fiber gummies. Some reported success with these therapies while others found that most supplements stop working after three months.

*“And so far on the oral medications, he's mostly taking just supplements, zinc, vitamin D.”* - Eric, father of a 27-month-old newly diagnosed son living with PMS

Carla was surprised to find that biotin helped improved her daughter's autism symptoms including eye contact, greater awareness and focus. *“I came back home and she immediately acknowledged me, looked at me, smile at me . ...She doesn't speak, but she was totally acknowledging me...And I'm like, [Oh my gosh, this is a totally different girl'. ...This is one of the few supplements that I've been giving her for more than three months, and the effect haven't disappeared yet.”* Carla F., mother of a four-year-old daughter living with PMS

*“We introduced a zinc treatment which has helped her concentration and general well-being.”* - Sandra, mother of a 24-year-old daughter living with PMS

*“In her short life span, I've tried everything, from supplements to medicine to vitamins, herbs, anything that you can imagine. If I have to pick what has really, really helped me, I would probably say I would be inclined to some of the supplements. Some of the supplements help. And also probably after three months, stop working.”* - Carla F., mother of a four-year-old daughter living with PMS

### **Mediations for GI issues including constipation and reflux**

Medications for GI issues include MiraLax, Pepsa, lactulose, Citrucel, linaclotide, Dulcolax, liquid magnesium and in extreme cases, botox and prostate medication. Not all work very effectively and combination approaches, including medications and diets are often required. Many parents mentioned having to regularly administer enemas to address constipation issues.



*“Chase also has constipation issues and we tried fiber, smoothies and a very clean diet. That didn't work, so we decided to use MiraLax, and now after 13 years, he is still taking a half cap of MiraLax every day in a smoothie.”- Angie, mother of a 13-year-old son living with PMS (Class I deletion)*

*“She has prunes every day, drinks prune juice every day, and then takes a mix of MiraLAX and Citrucel, both. She can't do full MiraLAX, because it makes her two gassy. So we just do a little tiny bit of MiraLAX. Five Senokot® tablets, two stool softeners, and a fiber supplement. And all that, and we can finally poop every day. Success.” - Cynthia, mother of a 19-year-old daughter living with PMS*

*“Ricky has been having issues with constipation. The GI doctor prescribed Lactulose and after six months on the medication, we felt that we were getting nowhere.” - Lisett, mother of an 11-year-old son living with PMS (SHANK3 variant)*

*“My son struggles with GI motility problems, and there are really no good options. We currently use Linzess but it doesn't help the root problem that stool backs up and doesn't make progress through the colon, leading to significant pain, rectal stretching, bloating and explosive bowel movements. This lack of signalling impacts his bladder as well, causing his bladder to store large amounts of urine, again causing pain, bloating. We are currently doing Botox on his sphincter as well as using a prostate medication as a relaxant, but it does not work well, and he is in constant discomfort.” - Laura, mother of a 22-year-old son living with PMS*

### **Sleep medications**

Sleep medications that were suggested include melatonin, guanfacine, clonidine, 5-HTP, GABA, trazodone and doxepin (anti-depressants), Xanax, Belsomra (Suvorexant), Ambien, cannabis and cannabis-derived products, and OTC sleep medications. Many parents are desperate for sleep – not only for their child with PMS but for themselves and other family members.

*“Chase didn't sleep more than two to three hours a night for eight years. We did a sleep study and a neurologist at UCSF prescribed melatonin and guanfacine and it worked. After eight sleepless years for my husband and I and Chase, he slept eight hours straight from age eight until now, age 13.” - Angie, mother of a 13-year-old son living with PMS (Class I deletion)*

*“For sleep, I've tried so many things, ...I tried 5-HTP, GABA, different roots, different sleep medications, you name it. Just tell me the name, I'll tell you I tested it. ...Melatonin has been one of those ones that has helped me at least get her to sleep.” - Carla F., mother of a four-year-old daughter living with PMS*

Mary has tried, “CBDs, Xanax, weighted blanket, pot brownies, for sleep. My husband and I take turns at night getting up with her.” - Mary S., mother of a daughter living with PMS

Addressing sleep issues often helps other symptoms including seizures.

*“Putting her on a small dose of trazodone helped enough to get her to sleep at night, and then once we started to get her to sleep at night, we did see the lorazepam working a lot better.”* - Cynthia, mother of a 19-year-old daughter living with PMS

Lisette went through extremes to treat her son’s sleep and seizure issues. *“After a year of treatments, which included five sessions per week of neurofeedback, three weekly visits to the chiropractor for body adjustments, and monthly visits to his neurologist for medication management, which included Briviact, Epidiolex, clobazam, clonazepam, valproic acid, the changes were clearly visible. Ricky began sleeping through the night and would only have sleep disturbances four nights each month. Other areas that we noticed improvement were that his seizure activity was stabilized, his eye contact had improved, asthma was under control, eczema had cleared, posture had improved and he had gained gross motor skills.”* - Lisett, mother of an 11-year-old son living with PMS (SHANK3 variant)

A downside is that sleep medications can help children fall asleep but not stay asleep, and they stop working after awhile.

*“We've been through the gamut of all sleep medication. I think we've tried six different ones. And none of them have fully helped. ... Nothing that gives her or our household a solid eight hours of sleep. So it makes treating anything else seem impossible when you're functioning on no sleep.”* - Ellie, mother of a seven-year-old daughter living with PMS

*“My son ...really didn't sleep at all through the night till age 4 when we started melatonin. That worked for several years. Later we tried clonidine, trazadone, and most recently doxepin. After several years, each medication stopped working. We have also tried and failed Belsomra and Ambien.”* - Laura, mother of a 22-year-old son living with PMS

### **Behavioral/psychiatric medications**

Many individuals living with PMS requires combinations of many different behavioral or psychiatric medications including antipsychotic/neuroleptics, sedatives, and others. They listed Risperdal (risperidone), Abilify (aripiprazole), Klonopin (clonazepam), Seroquel (quetiapine), Ativan (lorazepam), trazodone, hydroxyzine, anafranil, olanzapine, ADHD medication, SSRIs, lithium. Some parents described how these medications helped their children.

*"Better living through chemistry" is our motto. When my daughter first developed mania as a teenager, she didn't yet have the diagnosis of PMS. We went through every single drug for bipolar disorder available (except clozapine). After almost two years, she ended up on a combination of lithium, carbamazepine, olanzapine, and divalproex. She wasn't quite back to "normal" but was able to go to school, do sports, have fun." - Susan, mother of a 35-year-old daughter living with PMS*

*"She is diagnosed as being bipolar. ... She was manic at times to where she would be chattering and she would seem anxious. She couldn't sit still. She was constantly moving around. So the medication helped with that to where she would seem calmer, able to focus on what was going on." - Michael, father of a 38-year-old daughter living with PMS, diagnosed only one year previously*

*Asa suffers profound anxiety and self-injurious behaviors. "No supplement seemed to help, even one we successfully used years before to treat less severe anxiety issues. Finally, after dealing with this and several trials of medications that did nothing or actually had made him worse, we found a medication that over time gradually reduced his anxiety to a manageable level. Asa is still anxious and easily becomes frustrated, and when he does, he still hits his head. ... but at least his anxiety is not triggered merely by leaving his bedroom." -Arturo, father of a seven-year-old son living with PMS (SHANK3 variant)*

Many parents worried about addiction, very high doses of medications prescribed and side effects. Parents described how dextroamphetamines caused psychotic episodes, Risperdal can lead to addiction and weight gain, Abilify lead to increased rage, aggression and seizures, and antipsychotics can cause catatonia.

*Each medication that Cynthia's daughter tried seemed to come with a side effect. "We'd start a med and then a few days later we'd be off of a med." She was prescribed lorazepam for severe anxiety. "In December we'll be two years that we've been on lorazepam. ... We have tried to get her off of the lorazepam by just doing small quarter of a pill dose decreases, and each time we do, we see that sadness creep back in. So, we're just really leery about what that future holds with that med." - Cynthia, mother of a 19-year-old daughter living with PMS*

*After recovering from an antipsychotic-medication-induced catatonia, Laura's son now is being treated with low doses of both Ativan and lithium "It took 11 days of IV Ativan to actually get him out of the catatonic state and to get him back to walking and moving again. ... It's been almost a year in December when he will have been on this low dose lithium. And thankfully we have our normal, sweet, loving kid back, which is honestly amazing." - Laura, mother of a 22-year-old son living with PMS*

*“She has reacted adversely to every antipsychotic, except Seroquel and it did not treat the symptoms for which it was given. SSRIs caused mania. Anticonvulsants did nothing. Aivan and then Klonopin have helped the most with anxiety, seizures and catatonia.”* - Shelby, caregiver of a 49-year-old daughter living with PMS, diagnosed at the age of 42

Several parents described using intravenous immunoglobulin (IVIG) as way to address psychiatric symptoms such as catatonia and OCD. Downsides: the treatment is only temporary, patients risk contamination from infected products, and administration can be challenging in individuals with PMS.

*“At 18, an episode of severe mania was accompanied by catatonia and a long first seizure and two hospital stays. She was given a new diagnosis of seronegative autoimmune encephalitis and monthly IVIG was added to her meds. On this new treatment, she went four whole years without a psychiatric episode and we hoped we were out of the woods.”* - Tesi, mother of a 22-year-old daughter living with PMS (SHANK3 variant)

*“The IVIG treatment is still being studied but each infusion wears off after a month, and while low, IVIG has its own risk of transferring to Matthew pathogen or virus from the blood product used.”* - Mike, father of a 21-year-old son living with PMS (Class II deletion, 7.74 mega bp)

### **Seizure medications**

Parents reported a third of individuals living with PMS require seizure medications including Lamictal, Keppra and 30+, Briviact, Epidiolex, clobazam, clonazepam, valproic acid, Banzel, nayzilam and Depakote. Many reported having some success with seizure medications, especially when improvements with one symptom improved others (seizures, sleep, mood).

*“We just finally put her on Keppra and we haven't had any of the gelastic seizure manic episodes in a long time. So, we're hoping we've had some resolve with that.”* - Hope, mother of a six-year-old daughter living with PMS

*“Gavin, 13, is epileptic. He uses Lamictal to keep them at bay. But it also helps tremendously with his mood stabilization.”* - Heather, mother of a 13-year-old son living with PMS

Others found seizure medications less efficacious and resorted to increased dosages and combinations of medications.

*“She was treated with Keppra for several years, until breakthrough seizures led her doctor to add Onfi. Once seizures started breaking through again, we tried adding Lamictal, but its side effects were too great. We recently added Banzel, but even with three medications, seizures are still uncontrolled. We will be trying the ketogenic diet in*

*the coming months and if that too is unsuccessful, we will discuss surgical options.” - Lacy, mother of a nine-year-old daughter living with PMS (Class II deletion)*

*“We started using clonidine, she definitely sleep better but her seizures didn't stop. We started using Keppra and she didn't have a seizure for five months. However, seizure started again when new school year started. Doctor increased the dose from five milligrams to 750 milligrams. Seizures kept happening at school but not at home. Maybe there was too much stimulation at school. Maybe seizures are silent and short and I don't see them.” - Shiori, mother of a seven-year-old daughter living with PMS (Class II deletion)*

Other downsides of seizure medications include side effects like drowsiness and constipation, contraindications with other medications, a rigid and intensive administration schedule, and high doses. Rescue medications can suppress respiration, requiring their children to be resuscitated and are often administered rectally.

*“Onfi sometimes counteracts with other medicines like Epidiolex, you're not sure you can do Onfi. Or it also makes him sleep a lot, so he's sleeping sometimes 12, 14 hours a day.” Sue described how they tried reducing seizure medications but then her son experienced more seizures. “So we went back on and now he's on three meds, Onfi included, but he still sleeps a lot. But then of course, we think that adds to constipation and it's like it's connected, the seizures and the GI.” - Sue, mother of a 28-year-old son living with PMS*

Ethan was on very high amounts of Ativan. *“As a nurse, I question the high doses of Ativan for such a little boy where he is reviewing his rescue plan. For the first time, I feel the gravity of the situation when I'm told it's better to sedate and intubate Ethan. He's high risk for sudden death in epilepsy patients, SUDEP.” - Cathy, grandmother to a boy who died at the age of six from PMS (Class II deletion)*

### **Surgical procedures**

Parents described the different surgical procedures to manage PMS symptoms including the implantation of VNS and RNS devices for seizure control, gastric tubes for nutrition or rumination, scoliosis surgeries, tonsillectomies, corpus callosotomy and vesicostomies.

*“We've just had such a spike [in seizures] and such a difficult time trying to manage her epilepsy.” Jenny explained that they opted to implant a VNS which stimulates the nerve 30 seconds every five minutes. Jenny is hopeful that the VNS will mitigate the need for rescue medications and the inevitable 911 call that follows. “For us, the side effects are atrocious of the daily meds, but the rescue med side effects, which was stopping her from breathing, which watching your child be resuscitated is something I don't want to anybody else to experience. So that was really the call for us. If this could help us lessen*

*the use of rescue meds, then that's why we opted for this.*" - Jenny B., mother of a 16-year-old daughter living PMS

Ryan's son ruminates. *"When he was small ... we did the G-J tube placement because we were concerned with his nutritional value and him losing weight. We didn't place it because he couldn't swallow food, we were placing it because of the rumination to try to treat the rumination. ... He sent the message to us that he didn't like it, he started pulling it out."* - Ryan, father of a 13-year-old son living with PMS (terminal deletion, including all of the *SHANK3* gene

*"He had scoliosis surgery. Had a 75% curve, so he has two rods and 30 screws in his back. He's had hip surgery. ... The surgeries of course helped because without those, he'd be in major trouble."* - Sue, mother of a 28-year-old son living with PMS

*"He's undergone one surgery for an emergency tonsillectomy related to severe sleep apnea."* - Avis, mother of an eight-year-old son living with PMS

*"I don't think there is anything that I can pinpoint except for surgeries that help him, that he can stand and walk."* - Sue, mother of a 28-year-old son living with PMS

### **Medical marijuana, cannabidiol (CBD), Epidiolex**

Only a few selected medical marijuana, CBD or Epidiolex in the polls, but several mentioned using Epidiolex for seizures and marijuana for sleep.

*"Some of the treatments that we have tried, we either couldn't keep up with or didn't work out. For example, CBD made him cry."* - Lisett, mother of an 11-year-old son living with PMS (*SHANK3* variant)

### **Other medications not mentioned in the polls**

During the meeting, almost a quarter of parents and caregivers mentioned using other medications or medical treatments that they had used. These include recombinant human insulin-like growth factor 1 (IGF-1), botox for cyclical vomiting, birth control medications, bisphosphonate infusions for osteoporosis, antihistamines for allergies and to manage abdominal migraines, Adderall for incontinence, stem cell treatment, electroconvulsive therapy (ECT), reflux medications (Esomeprazole), autism medications (leucovorin), Parkinson's medications (carbidopa/levodopa), medications for hypothyroidism.

*"My daughter Lorena was medicated with IGF 1 Increlex for nine months and she had very good results. She improved in physical and mental skills, we stopped to make sure the improvements were because of IGF 1 treatment and we saw how many things went back and two years later we had it again for more than a year and we had again good results."* Lorena discontinued the drug because it interfered with her growth. - Norma, mother of a daughter living with PMS

*“We didn't talk about the pill, which is very helpful for girls to stabilise hormonal changes during puberty. It was essential for my daughter and helped treat the behavioural problems appearing then, together with Risperdone.” - Sandra, mother of a 24-year-old daughter living with PMS*

*Because of her son's cyclical vomiting, “Eventually decided to do Botox shots at the pylorus to relax the muscle so he wouldn't throw up. It worked for six months, but it came back, so we did it again and it didn't work the second time. ...Eventually, by age eight it did go away.”- Angie, mother of a 13-year-old son living with PMS (Class I deletion)*

Beyond medications and supplements, individuals living with PMS rely on a great deal of therapies to manage PMS-related symptoms.

Parents and caregivers used online polling to select the all the therapies and approaches - besides medications and medical treatments - that they had used to manage PMS-related symptoms. These are described below and in **Appendix 6, Q2**. The top approaches include speech therapy, occupational therapy and physical therapy.

**Many parents tried early intervention approaches with a combination of many therapies.** This was an important discussion point not captured in the polls.

*“At age 18 months, we were introduced to an early intervention program because Sammi didn't walk or speak. We started with physical therapy and occupational therapy and infant stimulation and group therapy were added. Age of four she was diagnosed with Autism Spectrum Disorder and also Dyspraxia Syndrome. Music therapy, hearing therapy and speech therapy and ABA therapy were added.” - Shiori, mother of a seven-year-old daughter living with PMS (Class II deletion)*

*“We started therapy at the age of eight months - the speech, the occupational, the physical. We didn't have a diagnosis so we didn't know. We just did therapy, therapy, therapy, just as much early intervention as we could.”- Martha, mother of a nine-year-old son living with PMS and a neurotypical twin*

Marie's son was diagnosed at 18 months old with autism. *“We started early intervention as soon as possible with therapies like the speech, therapy, OT, or APA therapies at these. I was noticing that he was not improving as much as I was hoping he would with an early intervention.” - Marie, mother of a 19-year-old son living with PMS (SHANK3 variant)*

### **Speech therapy (assistive speech device)**

Three-quarters of individuals living with PMS receive speech therapy and/or use assistive devices to support communication including augmentative and alternative communication

(AAC) devices and communication programs. They described different ones that had worked for their children, including the Spell 2 Communicate, PECS (picture exchange communication system), and PRM (rapid prompt method). Some parents were surprised to find that their children had stronger language comprehension than previously expected.

*“Josh is non-verbal. He communicates through the TouchChat app on his AAC device and he’s making progress there. He’s still mostly using it to request favorable songs, TV shows or food. We’re trying to model on his device with the hope of getting him to use it more openly for communication, rather than just requesting things.”* - Albert and Valentina, parents of an eight-year-old son living with PMS

*“His very poor receptive language makes it very hard for him to gain expressive language, even with AAC, augmentative and alternative communication. He has a manual dexterity to operate a screen just fine, but his limited receptive language makes it very hard for him to branch out beyond learning to use AAC to do more than request a few items.”* - Arturo, father of a seven-year-old son living with PMS (SHANK3 variant)

*“Sloan is using her AAC iPad device to use words to communicate. Her Registered Behavior Technician at her ABA center presented her with some letter cards and we learned that Sloan already knew her alphabet, but she had never had a way to communicate that and she learned it from watching YouTube videos. And so it's been interesting and eye-opening to see that she does understand some things and she does learn.”* - Jenn, mother of a seven-year-old daughter living with PMS

*“Recently, we started RPM, and learned that Chase is an excellent speller and can read and write. We are shocked as being non-speaking, he couldn't express himself and tell us what and how much he knows. It was a life-changing experience. So we will continue with this method of communication with him and the end goal is to get him to type so he can better communicate his thoughts and dreams.”* - Angie, mother of a 13-year-old son living with PMS (Class I deletion)

*“Their happy home is covered with laminated Velcro squares in the bathroom for hand washing, teeth, brushing, bath. On the fridge for his favorite foods. On the TV for his favorite shows. There are binders with more pick options, the system he's learned to communicate.”* - Cathy, grandmother to a boy who died at the age of six from PMS (Class II deletion)

*“She uses a communication device and goes to an inclusive mainstream school. We are pushing her to become literate.”* - Penny, mother of a six-year-old daughter living with PMS (Class II deletion)

*“Tallulah's socially driven personality, & willingness and ability to participate have made her constant involvement in therapies (since eight months old) very successful. Especially*



*oral-motor (PROMPT<sup>5</sup>) at a very young age, and occupational therapy to help integrate the sides of her brain. she responds well to aqua therapy for her physical challenges as well as for the regulating nature of being in the water. She loves therapies and with the proper motivators in place, has great success.” - Teresa, mother of a 16-year-old daughter living with PMS*

Speech therapy challenges: trained therapists are hard to find, and some patients don't have the required skills or cognition to operate AAC devices. For other patients, a pre-existing issue (constipation or discomfort) can interfere with therapy.

*“She has an AAC device for communication, but cognitively she's not where she can communicate, and physically she can't isolate her finger yet. So, a lot of times she's just kind of slapping at the screen. So, we still are unsure of what she wants.” - Hope, mother of a six-year-old daughter living with PMS*

*“We have tried several communicative AAC devices, PECS, signing, but nothing has worked.” - Martha, mother of a nine-year-old son living with PMS (two SHANK3 variants)*

### **Occupational therapy**

Similar to speech therapy, occupational therapy (OT) is part of a large suite of therapeutic approaches employed by many parents.

*“The services that have remained consistent for the last eight years are OT, PT, behavior therapy and speech therapy. It's very clear to me that the benefit of these services outweigh the sacrifices I'd have to make.” - Lisett, mother of an 11-year-old son living with PMS (SHANK3 variant)*

*“Currently the only treatment for hypotonia or joint and ligament laxity are physical and occupational therapy and sensory stimulation. Avenly has been in therapy since she was six months old, attending 10 hours a week for the past six years, including aquatic and hippotherapy. We also work at home and she spends three hours a day in a standing frame.” - Lacy, mother of a nine-year-old daughter living with PMS (Class II deletion)*

*“His gross and fine motor skills were highly impacted and he couldn't hold anything in his hands. We also began OT to improve his fine motor skills, like his pincer grasp, holding a pencil or anything in his hands.” - Angie, mother of a 13-year-old son living with PMS (Class I deletion)*

### **Physical therapy**

Physical therapy (PT) and other related therapies including swimming and horseback riding are used by 65% of individuals living with PMS. This has worked for some, but needs to be continuous or the benefits will be lost.

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<sup>5</sup> PROMPT is a system of physical cues for speech production.

By six months, *“Chase wasn't hitting any of his milestones, so he started the physical therapy for his low muscle tone. He had no real sense of balance and couldn't sit up on his own. PT started working on his balance, but we also worked on trying to walk.”* - Angie, mother of a 13-year-old son living with PMS (Class I deletion)

*“We have tried many therapies and the ones that have worked best for him have been aquatic and with horses.”* – Juan Francisco, parent of a son living with PMS

*“We did 17 years of speech and OT, and while many small gains occurred, the level of increase was minimal for the number of hours. We did Hippotherapy for core strengthening, posture control and balance, which did more than many years of PT. However, regression is a real issue, so once a therapy is stopped gains can be lost if not worked on at home continually.”* - Laura, mother of a 22-year-old son living with PMS

*Big impact on her motor skills has been seen with MAES (Movement Analysis and Education Strategies) therapy.”* - Penny, mother of a six-year-old daughter living with PMS (Class II deletion)

### **ABA Therapy**

Applied behavior analysis, or ABA, is often used for children on the autism spectrum to improve their communication, adaptive skills, and social abilities. Less than half reported using this approach yet there were many comments about this approach, with many saying that this was successful for their child.

*“I choose the ABA clinic which offered her occupational and speech therapy together; they work as a team. Special ABA works well. She's learning how to behave and express herself.”* - Shiori, mother of a seven-year-old daughter living with PMS (Class II deletion)

*“She started ABA Therapy (approx. 30-35 hours per week) when she was 3 years old, and we have never stopped. Many of the skills she lost in the regressions have taken months, if not years to regain. A few have yet to return – such as imitation, pretend play, age-appropriate motor skills, etc.”* - Anna, mother of a seven-year-old daughter living with PMS

*“We have been using ABA for a few years. We are uncertain of how effective it is.”* - Greg, father of a 9-year-old daughter living with PMS

*“The treatment that has helped the most is ABA both from help with behaviors, but more in the breaking down of learning activities (ADL's and other) into small pieces to help my son learn them. ABA has been amazing at teaching my son to tolerate the dentist working in his mouth, and not eloping in public (he was taught to either hold an adult hand or hold the cart in a store to avoid wandering off).”* - Laura, mother of a 22-year-old son living with PMS

### General diet modification (gluten free, lactose free)

Almost half of individuals with PMS had tried general diet modifications, but there were few comments. Some had tried FODMAP diets, ketogenic diets, others had a mixed experiences restricting gluten, sugar, soy and dairy.

*"We did find a regimen that worked, but you wouldn't believe what it took. So we put her on a FODMAP diet, which is basically gluten free, dairy free for her and a lot of fruit. She has fruit with every meal. She has prunes every day, drinks prune juice every day, and then takes a mix of MiraLAX and Citrucel, both."* - Cynthia, mother of a 19-year-old daughter living with PMS

*"Gluten-free diet didn't show any benefits."* - Lisett, mother of an 11-year-old son living with PMS (SHANK3 variant)

*"Removing dairy from Josh's diet helped eliminate his reflux. Removing most grains, gluten and sugar seems to have helped us well. ... We eventually even limited most fruit because of the sugar as well. ... We used to give him gluten free pasta and bread but then saw a difference in his sleep and behavior when we eliminated that too."* - Albert and Valentina, parents of an eight-year-old son living with PMS

*"Keeping her on a gluten-free, casein-free, soy-free diet. Low sugar, mildly low carb, clean diet that addresses nutritional approaches for the autism brain seems to have helped her thrive."* - Teresa, mother of a 16-year-old daughter living with PMS

### Supportive and personal equipment

Almost a third of individuals living with PMS rely on ankle foot orthotics, hand braces, back braces and other personal equipment for postural alignment or personal protection, including helmets, head protector beanies or headbands. A similar proportion require wheelchairs, walkers or strollers. These offer support, protection and/or mobility, but no long-term benefits. Many other personal equipment required by many with PMS include cooling vests for temperature regulation, standing frames to allow hips and legs to remain strong and grow properly. Most require diapers.

*"Avenly wears custom ankle foot orthotics or ankle stability. She wears a TheraTog, an FDA approved garment that gives individuals with sensory motor impairment improved postural alignment and stability. She also uses Venix wrist splints and kinesio tape. These bracing options offer additional support while in use but offer no long-term benefits."* - Lacy, mother of a nine-year-old daughter living with PMS (Class II deletion)

*Chase used a walker from age 18 months until he could take his first steps at 24 months. He would always fall like a tree and hit his head if someone wasn't behind him."* - Angie, mother of a 13-year-old son living with PMS (Class I deletion)

*“At school he has many aids to strengthen his muscles additionally: Standing device, running device, therapy bike.” - Sabine, mother of a 16-year-old son living with PMS*

### **Other approaches selected in the polls**

Other approaches selected in the polls including feeding therapy to train individuals to eat, lymphedema specific treatment including compression socks, intermittent lymphatic massage, and leg compression pumps. They also selected complementary therapies, and not doing anything to manage symptoms.

*“We began speech therapy due to his delayed speech and feeding therapy as he always would overstuff his mouth with food and would choke.”- Angie, mother of a 13-year-old son living with PMS (Class I deletion)*

*“We manage his lymphedema with compression socks and intermittent lymphatic massage. He wears braces for his varus ankles.” - Mike, father of a 21-year-old son living with PMS (Class II deletion, 7.74 mega bp)*

*“She currently does not receive any non-medical therapies, but when she was younger, she got speech therapy, occupational therapy, physical therapy, and all of those helped dramatically. But then, Phelan-McDermid took over and she regressed and she lost basically all of that development.”- Michael, father of a 38-year-old daughter living with PMS, diagnosed only one year previously*

### **Other options not mentioned in the polls**

Other non-medical approaches that were discussed at the meeting and in the comments are listed below.

**Adaptive strategies.** Parents described their strategies for helping to support their children including routines, distractions, and favorite videos to help engage their children living with PMS. Some had exit strategies for when in public.

*“Our family activities always needed an easy 'exit plan'. And we only ever considered family activities we could confidently attend with Jo.” - Gail, mother of a daughter who passed away from the complications of PMS*

*“He's so routine oriented. ...So, the five days of school, he's in a routine, generally he's good. Those are good days, he comes home tired, he relaxes. Saturday comes around and he's not happy because his routine is off. So, trying to replicate routines and keep things consistent for him is absolutely helpful.” - Carla D., mother of a seven-year-old son living with PMS*

*“To manage Sam's PMS, we stick to a fairly strict routine. We don't try to push him beyond his comfort zone. It feels like we are just trying to survive.” - Shelley T., mother of a 20-year-old son living with PMS*

**Home modifications including security cameras and door locks.** Many used these to monitor their children for seizures or to ensure that they didn't elope. Some used protective bedding to prevent their children from falling out of bed at night when they had seizures and some padded the edges of all the furniture and used non-breakable glasses and table wear.

*“Cameras are mounted so he is constantly visible, in the living room and on Ethan's cozy bed, which is a tented mattress on the floor for safety.” - Cathy, grandmother to a boy who died at the age of six from PMS (Class II deletion)*

*“We put many measures into place since to protect him. We've got pull alarms on every exterior door, handle locks. We've alerted all the neighbors.” - Avis, mother of an eight-year-old son living with PMS*

*“Our son's bedroom only contains two twin beds and a removable curtain rod for safety reasons. Either my husband or I sleep in his room to ensure he is safe as he is at risk of elopement and because he rarely sleeps through the night. At times we have to remove lamps TV, picture frames, and any other thing that might be within reach in every room of our home if he loses his ability to control his body.” - Kristine, mother of a 22-year-old son living with PMS*

*“Our Ivy-Rose requires 24hr care, needs assistance from adults and equipment all day and night, ... hoists, an indoor lift, an accessible shower room, a sleep system, AFO's and more.” - Inez, mother of a four-year-old daughter living with PMS (8.7 mb deletion)*

## **Service dogs**

Carla described that being able to participate in events as a family has, *“improved a bit since we've gotten his service dog, ... I think that it's the companionship and comfort of having the dog to lay on.” - Carla D., mother of a seven-year-old son living with PMS*

Other treatment approaches that were mentioned include Quantum Reflex Integration (QRI) mat and lasers for constipation, awareness and reduced nocturnal seizures, neurofeedback to reduce seizures, dolphin-assisted therapy, family-centered early developmental intervention, and sensory integration therapy.

Current approaches are not very effective, some have side effects and require much time and effort.

Parents and caregivers used online polling to first indicate how well their current treatment regimen treated the most significant symptoms of PMS, and then to select the top three drawbacks of their loved one's treatment regimen. Poll results are presented in **Appendix 6, Q3**

and Q4 and were fairly consistent with each other. Despite the intensity of therapies, Q3 poll results showed that the majority (91%) of parents and caregivers thought that their loved ones' treatment regimens worked very little or somewhat to address the most significant symptoms of PMS. The top downsides, in the Q4 poll results, were "only treats some, not all symptoms", "not very effective at treating target symptoms" and "side effects".

### **Only treats some not all symptom(s) and not very effective at treating target symptoms**

Outcomes for individuals with PMS are discouraging despite all the medications, the intensive therapies and different approaches. Regression negates the benefits of therapy and sometimes therapists drop children for their lack of improvement. Even if a child shows an improvement, sometimes it is hard to know if that is a result of the therapy or the result of natural development.

*"He's done every therapy known to mankind and he has a very limited skill set. ...I would say on the spectrum of PMS, he's very severely affected."* - Heidi, mother of an adult son living with PMS.

*"He hasn't stopped therapy. We've continued with everything; physical, occupational speech and ABA therapy. He's at a special needs school. And even with all this at the age of nine, he's still non-verbal."* - Martha, mother of a nine-year-old son living with PMS

*"Due to the lack of speed of progression, he's been dropped by multiple therapists and when they're dropped, these PMS kids have further regression. We had to find another facility for him to receive therapies, and recently he's been dropped again for the same reason, so we're currently searching for therapists."* - Avis, mother of an eight-year-old son living with PMS

*"And then he'll learn one skill. He started signing 'all done', but then he lost the ability to sign more. So it always feels like it's one step forward and two steps back."* - Megan, mother of a one-and-a-half-year-old son diagnosed when he was four weeks old

*"With my PMS child, there is no end in sight. We can talk about all of the symptoms and problems, but the truly hardest part the knowledge that there is no end to any of this. I don't know that he will ever be able to sit, eat, walk, talk (or even communicate). We have done and continue to do all of the therapies since he was 4 months old."* - Dottie, mother of a five-year-old son living with PMS

### **Side effects**

Almost half of parents selected side effects as one of their top three treatment downsides. These were described along with the different medical approaches earlier in the report, and with more quotes below.

*“We tried various forms of antipsychotics. They all had really serious side effects. And many of them escalated this behavior and made the aggression worse.” - Laura, mother of a 22-year-old son living with PMS*

*Seizure medications have many side effects. “Avenly's most common are dizziness, headache, irritability, tiredness, loss of strength and energy, problems of coordination, mood and behavioral changes, sleepiness, difficulty swallowing, drooling, appetite changes, constipation, excessive movement, difficulty paying attention, problems with urination and loss of bone density.” - Lacy, mother of a nine-year-old daughter living with PMS (Class II deletion)*

*“When we give the rescue med for seizure longer than two minutes, we have to call the ambulance because [rescue medications] depresses respirations. Life is scary because when Ethan would wake up in the hospital, he'd just be discharged with a med adjustment sometimes or sometimes not.”- Cathy, grandmother to a boy who died at the age of six from PMS (Class II deletion)*

*“My child with PMS for years was treated with Risperdal, Haldol, Invega, Lithium. These medications caused significant episodes of aggressive behaviors much worse than the behaviors we were trying to correct. The only option we were given was raise the dosage until things eventually got so bad that the doctors would change meds.” - Kelley, mother of a 29-year-old son living with PMS*

During the meeting, some described their worries about their children becoming addicted to medications, and the challenges of coming off the medications.

*“The Ativan is addictive, with its efficacy often diminishing over time.” - Mike, father of a 21-year-old son living with PMS (Class II deletion, 7.74 mega bp)*

*“It's also getting off things. Like we were on a medication one time for a year... We tried to get off for a year on Onfi just to see if that would help him. Of course, we had to go back on it because nothing else was helping him.” - Sue, mother of a 28-year-old son living with PMS*

### **Requires too much effort or time commitment**

This treatment downside generated many comments, as parents described the challenges of so many therapies and needing to balance this with work and other commitments.

*“He has a team of over 11 specialists and five therapists. He has required so much time in medical interventions, that only one parent in our household can work.”- Avis, mother of an eight-year-old son living with PMS*

*Our biggest concern is that most of the programs are aggressive about getting our daughter in as many hours as possible each week, more hours than we feel is beneficial to her. We are worried that she is treated as a profit center.” - Greg, father of a 9-year-old daughter living with PMS*

*“There's just not enough time to keep up with what he needs to do... We have on average anywhere from two to four appointments a week. ... We work full time and then we're supposed to go home and do PT, speech, and OT with him at home, but we also have another daughter that also deserves our time and attention. So it's just really difficult to balance our family time and all of the appointments and everything that he needs.” - Megan, mother of a one-and-a-half-year-old son diagnosed when he was four weeks old*

*“Much of my son's time is taken up with therapies, frequent doctors appointments, and long hospitalizations, which is very stressful to a non-verbal person who requires consistent routines.” - Laura, mother of a 22-year-old son living with PMS*

#### **Limited availability or accessibility and high cost or co-pay, not covered by insurance**

Parents described limited availability or accessibility and the high cost or copay or not covered by insurance as their top choices. They described a shortage of qualified therapists, gaps between what is needed and what can be funded, changes in formulation, COVID-19 limitations, patients aging out of the system.

*A new medication formulation no longer worked to control Michael's daughter's bipolar disorder. “She was on a thicker medication, which working really well. The manufacturers of those medications came out with second generation... it didn't work. We had great difficulty going back to the older medication because they weren't making it anymore.” - Michael, father of a 38-year-old daughter living with PMS, diagnosed only one year previously*

*“For a person like my son, services should be every day, eight hours a day. So, that's very difficult financially for families like us to be able to provide the finance to support therapies for a person who has so much disability. And I couldn't work myself because I became pretty much a caregiver for my son. So, that really did impact our family in the financial point of view, and also other points of view.” - Marie, mother of a 19-year-old son living with PMS (SHANK3 variant)*

*“Once she was out of school for COVID she became very tight [due to lack of PT] causing her noticeable pain. She lost fine and gross motor skills. In the US, when your child ages out of the school system (~age 22) they are no longer receiving PT/OT/SLP in the school setting. Going forward any regular therapy will need to be paid out of pocket because US health insurance companies generally do not cover long term therapies. For families that can't afford decades of private, out-of-pocket therapies will watch their adult child lose*



*skills and have pain (tightness without PT).” - Megan, mother of an adult daughter living with PMS,*

*“My son gets monthly IVIG, which has helped greatly with his mania, though he does still cycle through monthly manic episodes, though they are reduced. I travel four hours one way and keep him overnight from his facility to provide these infusions as we have had issues accessing the care due to him being in a different state. We are looking at an insurance change in the upcoming year and I worry about our access to the IVIG when that change happens.” - Laraleigh, mother of an adult son living with PMS*

*“We tried to get growth hormone off-label for Bodhi’s PMS and the cost with Optum RX was \$42,000 for 1st fill. Insurance denied coverage since he didn’t have growth hormone deficiency in his medical records. These are the barriers to help for our kids.”- Jaimie, mother of an eight-year-old son living with PMS*

### **Large number of pills/medications**

A fifth of parents selected the high number of pills and medications as one of their top three downsides, and this was described throughout the meeting and in this report. Despite all these medications, nothing works.

*“My 24-year-old son has, on average, 10 or more seizures per day. That is despite the fact that he currently takes a cocktail of 5 different anti-seizure medications, has a VNS device, has undergone a corpus callosotomy, and has tried the low glycemic and ketogenic diets for epilepsy. Unfortunately, treatment failures have greatly outnumbered successes.” - Brad, father of a 24-year-old son living with PMS and LGS (Class I deletion)*

*“My son takes over 20 medications a day for seizures, gastro-intestinal motility issues, neurogenic bladder, sleep, behavior support, and several medications are simply to counter the side effects of some of the first medications. There is really nothing that treats the underlying problem of communication between his brain and his body that so often is not working.” - Laura, mother of a 22-year-old son living with PMS*

### **Other treatment downsides not included in the polls.**

Route of administration was a treatment downside mentioned often. Parents described the challenges in administering treatments. Route of administration was mentioned particularly for rescue medications, some which need to be administered rectally.

Mike described how sedation is required for IVIG treatments. *“Infusions take four hours, administered monthly and since Matthew can't sit still for 30 seconds, it means he will have to be sedated, which is always a worry.” - Mike, father of a 21-year-old son living with PMS (Class II deletion, 7.74 mega bp)*

Parents also described challenges with communicating medical information, both with specialists who didn’t know much about PMS or having to rely on second- and third-hand information.

*“We had been working with some of the Phelan-McDermid doctors around the country to help provide some background to the psychiatrist to say what kind of medications were maybe contraindicated given his PMS diagnosis.” The treating physician was reluctant to accept the advice of PMS experts. “So they gave him very strong antipsychotics, which flipped him into a very severe catatonia. ... It became life threateningly dangerous and we had to have him evacuated to another hospital that would treat the medical side.” - Laura, mother of a 22-year-old son living with PMS*

Michael’s daughter is extremely manic but lives in a care facility, making medical communication between caregivers, parents, and medical professionals challenging. . *“It’s not clear exactly what’s happening because she has 24-hour one-on-one care but multiple people, and the way they assess what’s going on with her can be slightly different. They’re having a hard time managing it. We’re getting information second-hand. Her psychiatrist getting the information third-hand.” - Michael, father of a 38-year-old daughter living with PMS, diagnosed only one year previously*

In addition to treatment downsides, parents described the challenges of monitoring patients who don’t understand or won’t sit still.

*“We have done EEG three time in the past but never detected seizure. Sammi struggles with the EEG, tries to pull the leads off her head.” - Shiori, mother of a seven-year-old daughter living with PMS (Class II deletion)*

Short of a cure, parents would like their loved ones with PMS to have an improved quality of life.

Parents again used the online poll to select the specific things that they would look for in an ideal treatment for PMS, short of a cure. Results are shown in **Appendix 6, Q5**. Their top three choices for an ideal future treatment include improved cognitive functioning, improved communication and slowing or stopping disease regression. All of the choices presented in the polls would support and improve quality of life for individuals living with PMS.

*“We try to give her choices to pick from, to give her a sense of control of her life that has spiraled so horribly wrong the past two years. We work hard every day to keep her safe and try to make her comfortable. Her quality of life is what we want most for her. Please help find that magic pill to bring her back!” - Karen B., parent of a 22-year-old daughter living with PMS*

### **Improved cognitive functioning and increased independence**

Improved cognitive function was the top poll response option and was reflected in the many comments about wishes for neuroprotective interventions, improvement in basic life skills, independence and quality of life.

*“Amadi needs neuroprotective interventions to prevent the regression we dread, which is still so poorly understood. She needs better psychoactive and immunologic treatments to make her episodes less frequent and less severe so that she suffers less, and so she can live with friends in a group home singing a chorus and be of use in the world.”* - Tesi, mother of a 22-year-old daughter living with PMS (SHANK3 variant)

*“I just want my son to have a chance of having a better quality of life, to be able to self-feed, groom, dress, use the restroom and communicate with his AAC device independently. Basic living and life skills, all the little things that many of us potentially took for granted prior to having someone with Phelan-McDermid syndrome in our life. That's what I want for my son, all the little things that he was robbed from having.”* - Lisett, mother of an 11-year-old son living with PMS (SHANK3 variant)

*“If you ask what our hope is, it's that somehow we find a drug that helps him cognitively, even if he's in his 20s, so that he can take care of himself to a point (at least get dressed or use the bathroom on his own), and find ways to occupy his time when he doesn't have a structured task give to him by a teacher. We hope that we don't have to worry about leaving him alone in a room for more than 60 seconds, worrying that he can so easily hurt himself.”* - Albert and Valentina, parents of an eight-year-old son living with PMS

*“How can I make his life better and what kind of advancements can we have in the future to make these children be able to be more involved in things?”* - Ryan, father of a 13-year-old son living with PMS (terminal deletion, including all of the SHANK3 gene)

### **Improved communication**

Parents felt that improving their loved ones' communication would make an enormous impact on their lives.

*“I think my top preference is for future treatments is... communication, mobility, coordination, and cognitive functioning. If they could communicate better, I'd know what they're thinking, or if there's any pain, they could tell me where it is.”* Eric's comment about PMS children speaking with their eyes resonated with many at the meeting. *“At least from my kid, and even though he's only 27-month-old, his eyes are talking and I understand every time I look at him or he's looking at something, even though he doesn't point, I understand what he wants, right? ...I hope that the future treatment could help them express that through talking, then it would be a lot more helpful.”* - Eric, father of a 27-month-old newly diagnosed son living with PMS

*“I'm surviving on hope that one day I'll hear my daughter's voice. I know it will be beautiful.”* – Maureen, mother of a five-year-old daughter living with PMS

*“If there's a way to help my children so that they can be safe for their whole lives, or at least have the ability to say, “I'm not safe,” to understand that they're not safe, that*

*would be an amazing opportunity.” - Joanna, mother of a six-and-a-half-year-old son living with PMS*

*“It would be amazing for both Asa and us if he could even understand 50 words or a hundred words. 500 words would be a dream.” - Arturo, father of a seven-year-old son living with PMS (SHANK3 variant)*

### **Slowing or stopping disease progression or regression**

The third top choice for an ideal treatment is to stop or slow disease progression.

*“I would like to stop her disease progression. ... When she was two she had way tons more skills than she has today. She used to speak, she used to feed herself, she used to walk, she used to follow instructions. She used to do so many things that she cannot do today. Almost three years later. So for me that would be amazing, just that stop so she can continue gaining the skills and not lose them, that's all.” - Carla F., mother of a four-year-old daughter living with PMS*

### **Improved behavioral/psychiatric symptoms**

Parents described how improving this symptom could help others

*“Our hope is for a more effective long-term treatments for this kind of catatonia. ... Of course, we would love to have a total cure for PMS, maybe a way to insert the missing piece of his 22nd chromosome into each cell of the body, but I suspect that is still a ways off. Nonetheless, we remain ever hopeful.” - Mike, father of a 21-year-old son living with PMS (Class II deletion, 7.74 mega bp)*

*“An ideal treatment for Bennett would be to help with his impulsivity. This could help keep him safe.” - Avis, mother of an eight-year-old son living with PMS*

*“We'd like any medication that could make her calmer.” Michael, father of a 38-year-old daughter living with PMS, diagnosed only one year previously*

*“I wanted to improve the behavioral, the psychiatric symptoms and then the GI. I feel like those two alone would help lead for better cognitive function. And that would be most important to me, is better cognitive function too, because I feel like that might also help improve some of the mental health issues if they were cognitively just a little bit there.” - Cynthia, mother of a 19-year-old daughter living with PMS*

### **Improved GI function**

Many parents commented that if GI issues and seizures could be improved, cognitive function, would improve as well.

*“I chose three things that I think are connected. The seizures and the GI function. I mean, I think if you do something with one, you'll do something with the other. And then I think that applies to cognitive functioning. If they weren't as stressed and didn't have as many*

*GI issues and seizures, I think the cognitive functioning would be better.” - Sue, mother of a 28-year-old son living with PMS*

*“A treatment that we would want that doesn't exist is treatment for bowel and bladder motility. My son struggles to relax muscles due to dystonia, which impacts his colon, his bladder and his walking. ...Being unable to use the toilet independently at 22 years of age really impacts his every day life.” - Laura, mother of a 22-year-old son living with PMS*

### **Improved sleep**

Parents wished for improved sleep for their loved ones.

*“She just has not slept in three years. And that makes it impossible with three other kids to focus on really any other treatment.” - Ellie, mother of a seven-year-old daughter living with PMS*

*It would be amazing though for us if he could just regularly get a normal night of sleep.” - Arturo, father of a seven-year-old son living with PMS (SHANK3 variant)*

### **Improved mobility and coordination, including more body awareness**

Parents described wanting treatments to resolve hypotonia and lax joints and ligaments and to increase muscle tone.

*“Improving muscle tone would likely lead to Avenly being able to meet basic milestones like reliable, independent sitting and standing, walking, helping with transitions into the bathtub, wheelchair, or car seat. Treatments could also improve organ systems affected by hypotonia. ...Being upright and mobile might improve her respiratory function, digestion, circulation, bowel and bladder function and bone development. She could gain the strength to cough, blow her nose, or even initiate toileting on her own. These are all basic life skills many of us take for granted.” - Lacy, mother of a nine-year-old daughter living with PMS (Class II deletion)*

*“I would love for her to have some more ...awareness of where her body is in space. She trips over things, she runs into things, she doesn't seem aware enough, so she has to move. If I'm trying to put her clothes on, she's constantly stepping around in circles and doesn't have enough body awareness to stay still. ... So it's all interconnected, but body awareness I think would be at the top for me.” - Jenny B., mother of a 16-year-old daughter living with PMS*

### **Decreased seizures**

Parents would like some way to decrease the frequency and intensity of seizures and the risk of SUDEP.

Sue's comment resonated with other parents who also reiterated that they didn't want to lose their children to SUDEP. *“Well, the main thing is we want them to live. SUDEP is*

*real in our community. ...For me, that's the main thing.*" - Sue, mother of a 28-year-old son living with PMS

*"I'll be happy if there was a treatment for epilepsy, hypotonia, or little improvement for communication skill. That would be life-changing for Sammi and my family."* - Shiori, mother of a seven-year-old daughter living with PMS (Class II deletion)

*"Our future treatment goals would be hopefully focused on something that hit that population of PMS kiddos that have some sort of abnormality neurologically, but don't quite fit that criteria for seizure treatment."* - Ellie, mother of a seven-year-old daughter living with PMS

### **Other treatment considerations not included in the poll responses.**

While only a very small number of parents surveyed selected "other" treatment considerations, they made many treatment wishes during the meeting and in the comments. Some ideas included treatments for rumination, taking the whole spectrum of the PMS into consideration rather than trying to address one symptom at a time.

*"An ideal future treatment for our son would be a treatment for rumination. Our son, Carter, ruminates 100's of times a day. We have been to several GI motility specialists with no help. This highly disrupts his daily quality of life. There are currently no treatments for rumination on the market."* - Erica, mother of a son living with PMS

*"One of the things I'd like to see in future treatments, is that the providers take the whole issue of Phelan-McDermid together." Elizabeth listed some of the issues her daughter experiences which influence her treatment including the slower metabolism of drugs, side effect profiles, kidney damage and liver burden."* - Elizabeth, mother of a 24-year-old daughter living with PMS

Some asked for different administration options, especially changes for rectally- administered rescue medications.

*"We were in a clinical trial for a rescue med, for a nasal spray instead of doing rescue med rectally, and that changed our lives. Just using a nasal spray for a rescue med. ... so you can go outside and be on a bike and not worry that you have to throw them on the ground [to administer medication]."* - Sue, mother of a 28-year-old son living with PMS

Some asked for a reduction in medication side effects, especially for seizure medications.

*"Consider the side effects of current seizure medications. The impact this would have on our lives is truly understated."* - Lacy, mother of a nine-year-old daughter living with PMS (Class II deletion)

## Incorporating Patient Input into a Benefit-Risk Assessment Framework

The FDA uses a Benefit-Risk Assessment Framework which includes decision factors such as the analysis of condition, current treatment options, benefit, risk, and risk management. The Framework provides an important context for drug regulatory decision-making and includes valuable information for weighing the specific benefits and risks of a particular medical product under review.

**Table 1** speaks to the challenge of having a lifelong disease burden that patients living with PMS endure. It serves as the proposed introductory framework for the Analysis of Condition and Current Treatment Option to be adapted and incorporated in the FDA's Benefit-Risk Assessment. This may enable a more comprehensive understanding of this unique condition for key reviewers in the FDA Centers and Divisions who would be evaluating new treatments for PMS. The data resulting from this meeting may help inform the development of PMS-specific clinically meaningful endpoints for current and future clinical trials, as well as encourage additional researchers and industry to investigate options for treatments.

The information presented captures the perspectives of caregivers caring for patients living with PMS presented at the November 8, 2022, meeting. It also includes information from the polling results, as well as comments submitted before, during, and after the meeting through the online portal.

Note that the information in this sample framework is likely to evolve over time.

**TABLE 1 Phelan-McDermid Syndrome Benefit-Risk Table**

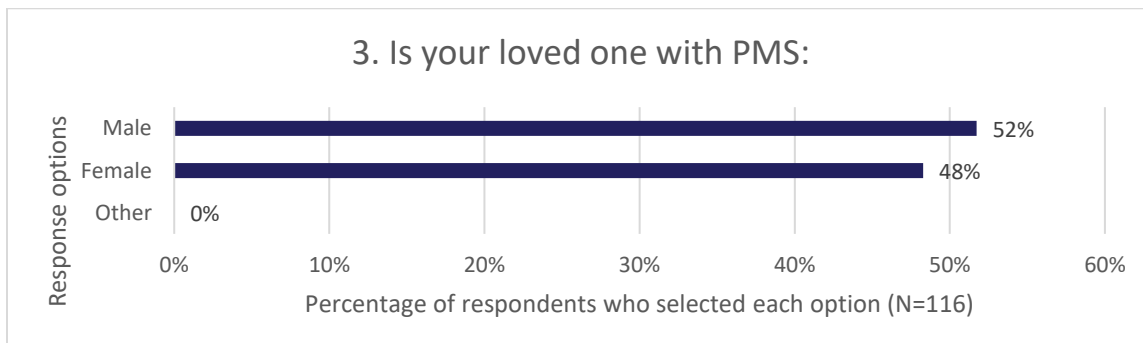
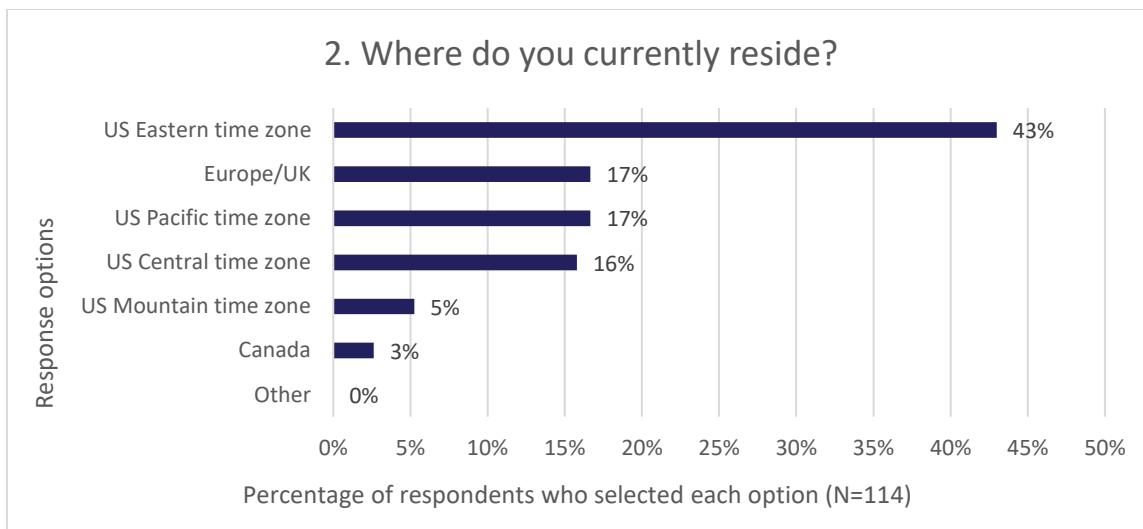
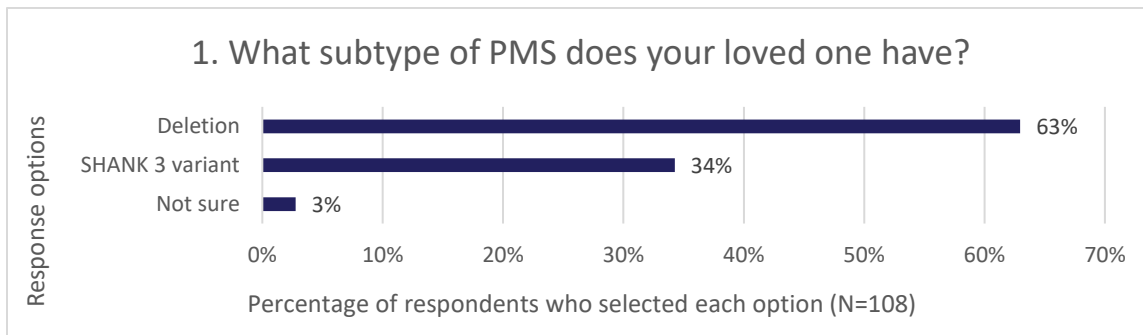
	EVIDENCE AND UNCERTAINTIES	CONCLUSIONS AND REASONS
ANALYSIS OF CONDITION/ IMPACTS ON ACTIVITIES OF DAILY LIVING	<p><b>Phelan-McDermid syndrome is a complex syndrome characterized by intellectual disability.</b> PMS is characterized by a wide range of abilities and disabilities, with the type and severity of symptoms varying from one person to another. Individuals living with PMS have a complex and interrelated constellation of symptoms.</p> <p><b>Regression is a common characteristic of PMS.</b> Children may lose many acquired skills including communication. While triggers of regression in PMS are not fully understood, older patients often experience regression after psychiatric episodes.</p> <p><b>Developmental delay and intellectual impairment are top health concerns followed by communication issues and muscle weakness,</b> however the list of PMS-related symptoms is exhaustive, and the impacts on quality of life are enormous.</p>	<p><b>PMS has severe quality of life impacts on patients, as well as on parents and siblings.</b> Most activities of daily life, including communicating needs or wants, self-care (and socializing with peers/siblings are affected. Most individuals living with PMS rely on their parents and caregivers for all their daily needs, and many require 24-hour care. Hospitalization is frequent for individuals with PMS. A lack of spatial and safety awareness can lead these children to danger.</p> <p><b>Parents and caregivers have many worries for their loved ones, especially about their future care.</b> They worry that their loved ones will be completely dependent on caregivers, that symptoms will only get worse, and their loved ones will be unable to communicate their health problems. Many parents fear losing their child prematurely.</p>
CURRENT TREATMENT OPTIONS/ PROSPECTS FOR FUTURE TREATMENTS	<p><b>There are no FDA approved treatments for PMS despite its severely debilitating manifestations.</b></p> <p><b>Patients require a lot of different therapeutic approaches.</b> Most individuals start receiving therapeutic interventions early in their childhood and continue throughout their lives.</p> <p><b>Existing therapies and medical treatments are not very effective.</b> They only address some, but not all of the symptoms, and many medications have side effects. Regression further negates the benefits achieved from therapy.</p>	<p><b>PMS has an overwhelming unmet medical need.</b> Parents and caregivers are open to trying almost anything to try to relieve their child’s suffering; most have tried an incredibly high number of treatments and approaches for symptom management, with very little success. Some received medications that caused more harm than good.</p> <p><b>Parents’ top priorities for benefits that new therapies could deliver:</b> improved cognitive functioning, improved communication, and preventing or slowing regression.</p>
	<b><i>See the Voice of the Patient report for a more detailed narrative.</i></b>	



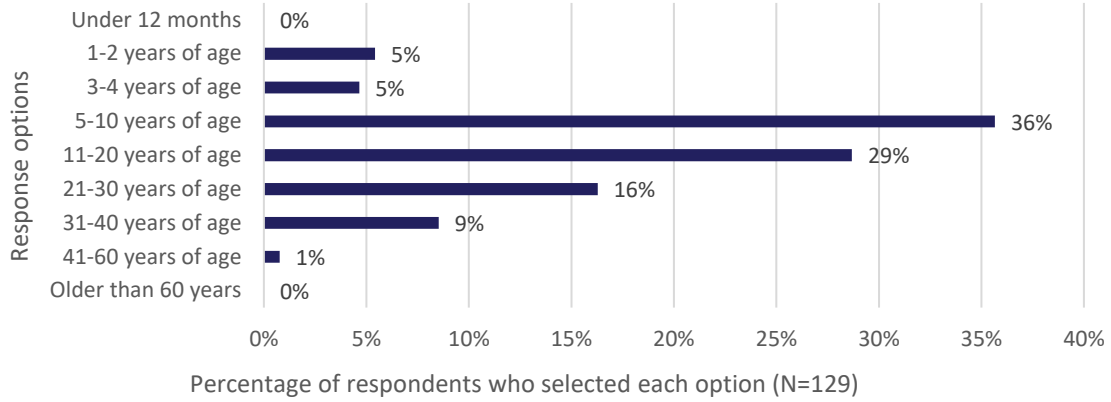
## Appendix 1: Demographic Questions

The graphs below include all attendees who chose to participate in online voting. Parents and caregivers were asked to answer the questions on behalf of the individual living with PMS. The number of parents and caregivers who responded to each polling question is shown below the X axis (N=x).

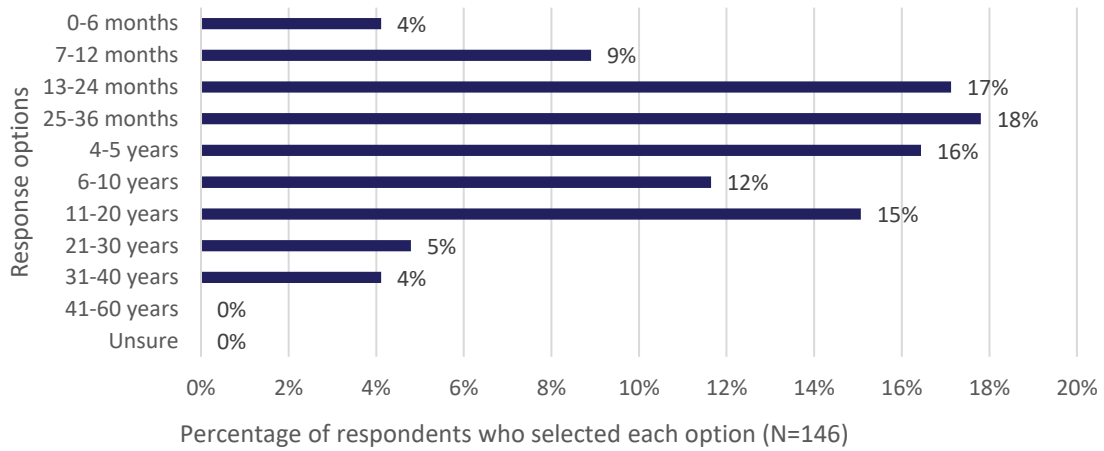
While the response rates for these polling questions is not considered scientific data, it provides a snapshot of those who participated in the PMS EL-PFDD meeting and is intended to complement the patient comments made during and after the meeting.



#### 4. What is the affected individual's age?



#### 5. At what age was the affected individual diagnosed with PMS?



## Appendix 2: Meeting Agenda

Phelan-McDermid Syndrome EL-PFDD Meeting  
Tuesday, November 8, 2022

- 10:00 am Welcome & Overview  
*Geraldine Bliss, CureSHANK*
- 10:05 am Opening Remarks  
*Dr. Wilson Bryan, FDA*
- 10:15 am Background on Phelan-McDermid syndrome  
*Dr. Alex Kolevzon, Seaver Autism Center at the Icahn School of Medicine at Mount Sinai*
- 10:30 am Introduction and Meeting Overview  
*James Valentine, Hyman, Phelps & McNamara*
- 10:35 am Audience Demographic Polling,  
*James Valentine, Hyman, Phelps & McNamara*

### **Session 1: Phelan-McDermid Syndrome Patient Voices: Symptoms and Daily Impacts**

- 10:45 am Panelist presentations
- 11:10 am Audience polling and discussion
- 12:30 pm Lunch break
- 1:00 pm Introduction to afternoon session

### **Session 2: Phelan-McDermid Syndrome Patient Voices: Current and Future Treatments**

- 1:05 pm Panelist presentations
- 1:30 pm Audience polling and discussion
- 2:45 pm Summary Remarks  
*Larry Bauer, Hyman, Phelps & McNamara*
- 2:55 pm Closing and Next Steps  
*Dr. Kate Still, Phelan-McDermid Syndrome Foundation*

## Appendix 3: PMS Meeting Discussion Questions (validated!)

### **Topic 1: Living with PMS: Symptoms and Daily Impacts**

1. Of all the symptoms and health effects of PMS, which 1-3 symptoms have the most significant impact on your loved one's life?
2. How does PMS affect your loved one on best and on worst days? Describe your best days and your worst days.
3. How has your loved one's symptoms changed over time? How has their ability to cope with the symptoms changed over time?
4. Are there specific activities that are important to your loved one that they cannot do at all or as fully as they would like because of PMS?
5. What do you fear the most as your loved one gets older? What worries you most about your loved one's condition?

### **Topic 2: Perspective on Current and Future Approaches to Treatment**

1. What are you currently doing to manage your loved one's PMS symptoms?
2. How well do these treatments treat the most significant symptoms and health effects of PMS?
3. What are the most significant downsides to your loved one's current treatments and how do they affect daily life?
4. Short of a complete cure, what specific things would you look for in a treatment for PMS? What factors would be important in deciding whether to use a new treatment?

## Appendix 4: Panel participants meeting speakers

### Session 1: Patient Testimonials

- Amanda, mother of a seven-year-old daughter living with PMS (Class I deletion)
- Arturo, father of a seven-year-old son living with PMS (*SHANK3* variant)
- Tesi, mother of a 22-year-old daughter living with PMS (*SHANK3* variant)
- Angie, mother of a 13-year-old son living with PMS (Class I deletion)
- Cathy, grandmother to a boy who died at the age of six from PMS (Class II deletion)

### Session 1: Discussion Starters

- Cyra, mother of an 11-year-old daughter living with PMS
- Jenn, mother of a seven-year-old daughter living with PMS
- Ryan, father of a 13-year-old son living with PMS (terminal deletion, including entire *SHANK3* gene)
- Joanna, mother of a six-and-a-half-year-old son living with PMS
- Carla D., mother of a seven-year-old son living with PMS

### Session 1: Callers

- Martha, mother of a nine-year-old son living with PMS
- Heidi, mother of an adult son living with PMS
- Chris, mother of a 22-year-old son living with PMS
- Marie (caller), mother of a 19-year-old son living with PMS (*SHANK3* variant)

### Session 2: Patient Testimonials

- Lisett, mother of an 11-year-old son living with PMS (*SHANK3* variant)
- Mike, father of a 21-year-old son living with PMS (Class II deletion, 7.74 mega bp)
- Shiori, mother of a seven-year-old daughter living with PMS (Class II deletion)
- Lacy, mother of a nine-year-old daughter living with PMS (Class II deletion)
- Avis, mother of an eight-year-old son living with PMS

### Session 2: Discussion Starters

- Carla F., mother of a four-year-old daughter living with PMS.
- Sue, mother of a 28-year-old son living with PMS
- Eric, father of a 27-month-old newly diagnosed son living with PMS
- Jenny B., mother of a 16-year-old daughter living with PMS
- Cynthia, mother of a 19-year-old daughter living with PMS

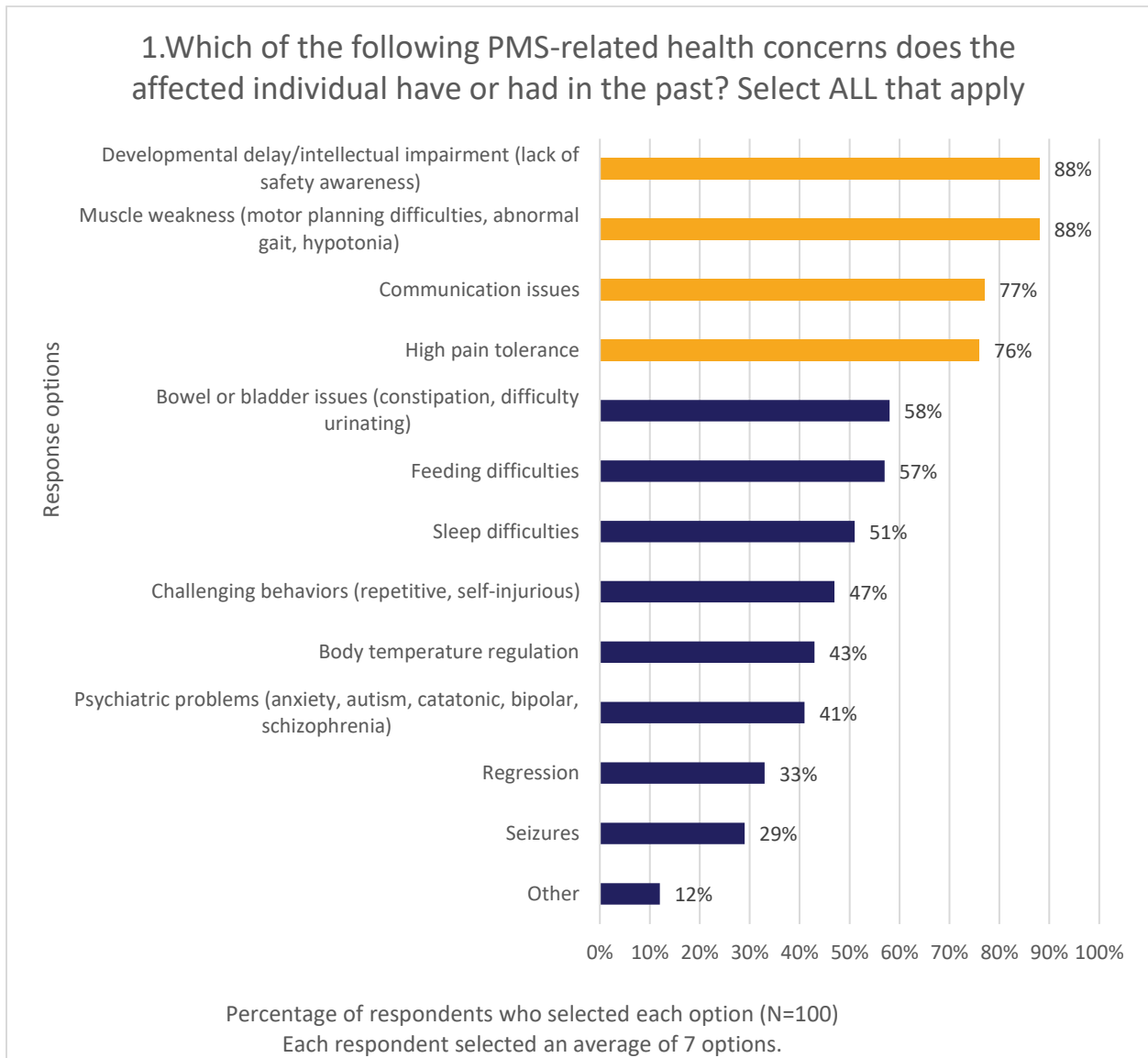
### Session 2: Callers

- Michael, father of a 38-year-old daughter living with PMS, diagnosed only one year previously
- Megan, mother of a one-and-a-half-year-old son living with PMS
- Elizabeth, mother of a 24-year-old daughter living with PMS
- Ellie, mother of a seven-year-old daughter living with PMS

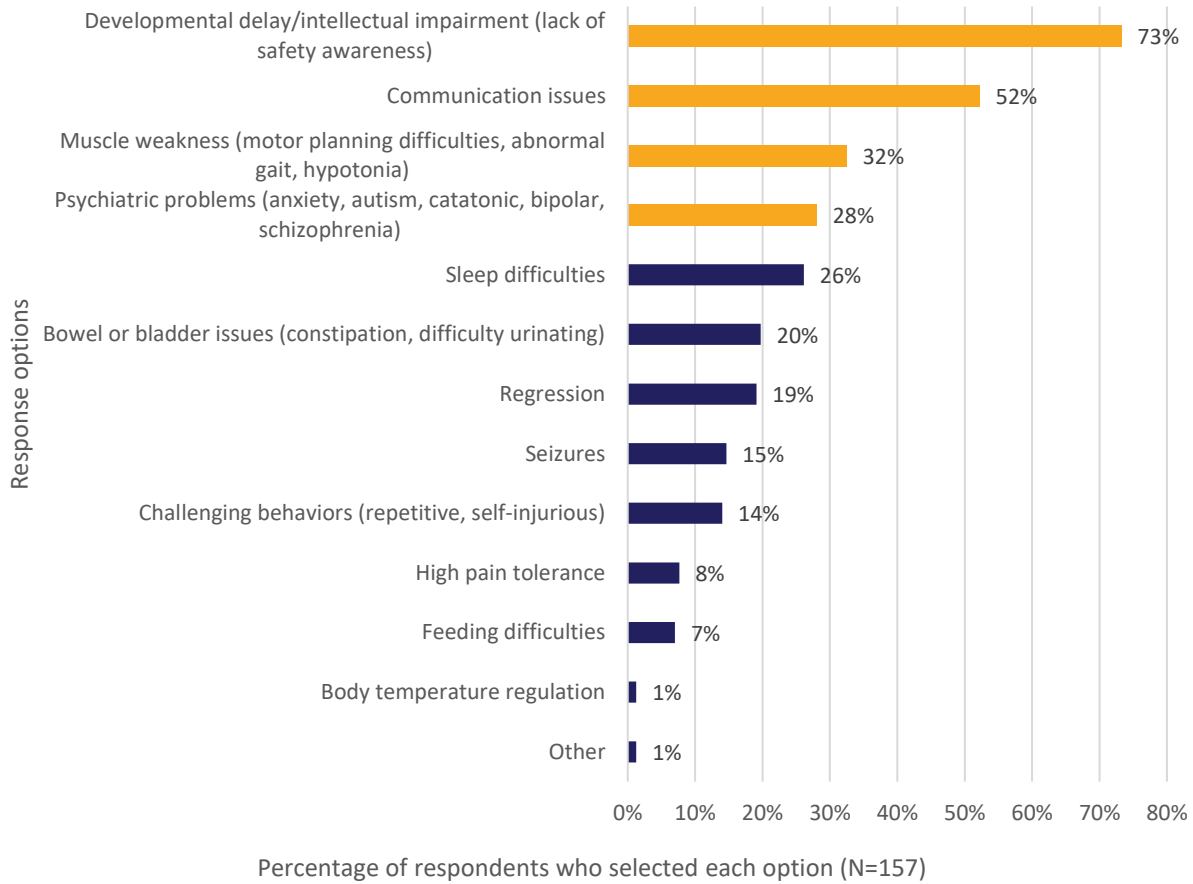
## Appendix 5: Session 1 Poll Results

The graphs below include all meeting attendees who chose to participate in online voting, who answered questions on behalf of their loved one living with PMS. The number of parents and caregivers who responded to each polling question is shown below the X axis (N=x).

The responses for these polling questions are not considered scientific data, but are provided to present a snapshot of those who participated in the PMS EL-PFDD meeting and is intended to complement the patient comments made during and after the meeting.

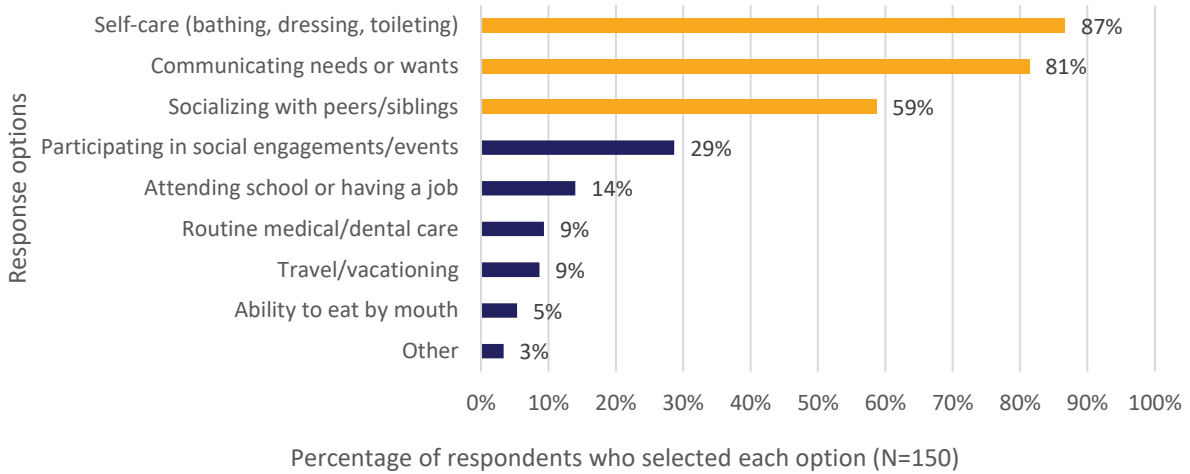


## 2. Select the most troublesome PMS-related health concerns that your loved one has ever had. Select TOP 3

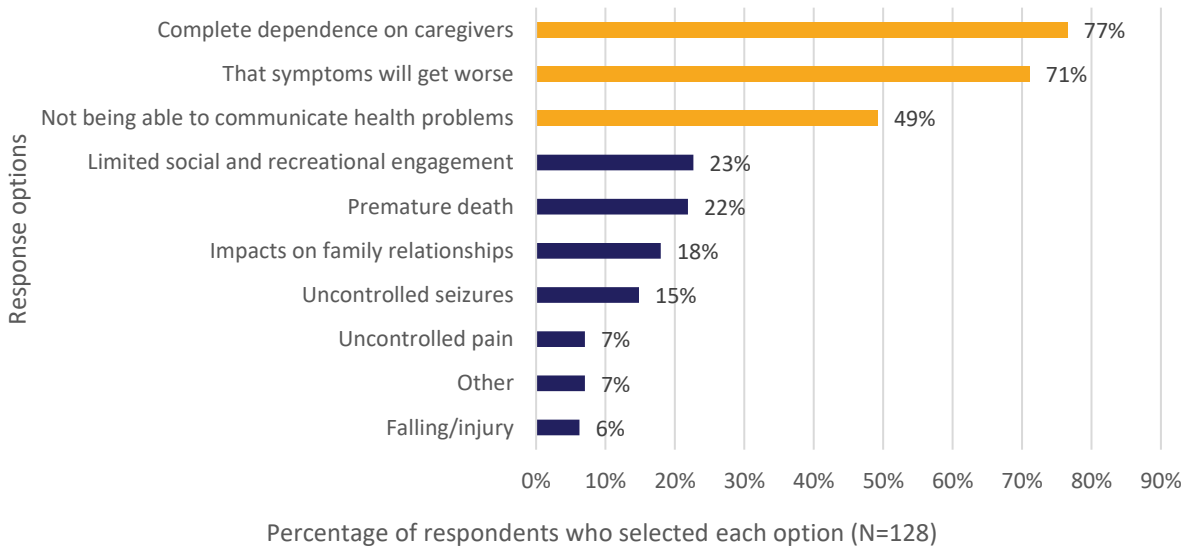




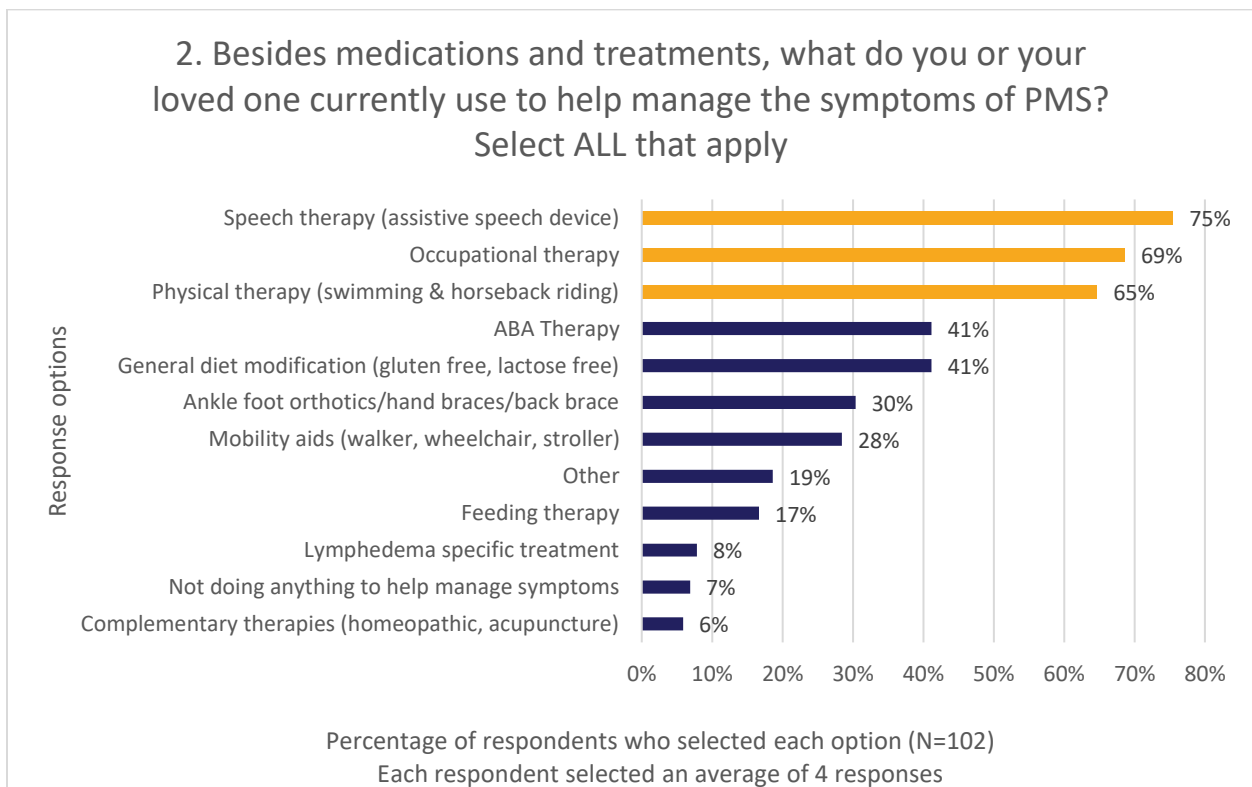
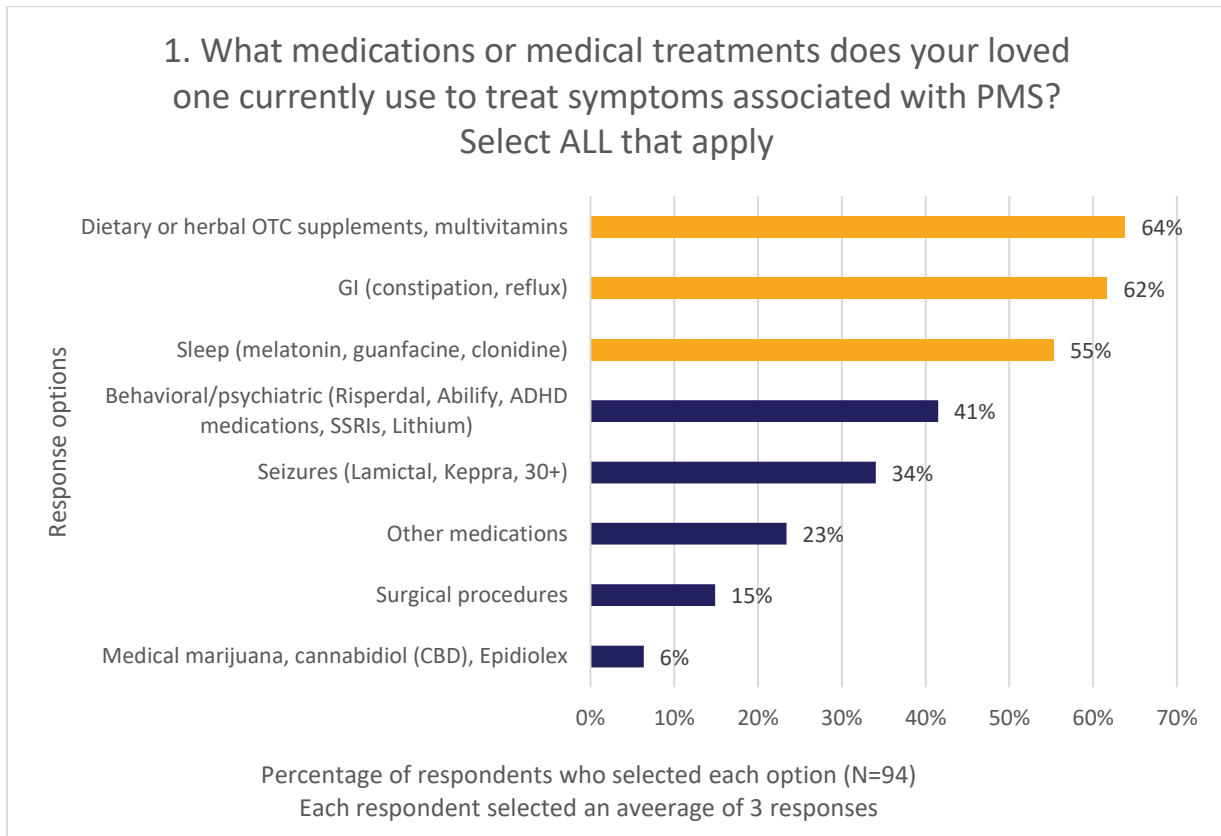
3. What specific activities of daily life are important that your loved one is NOT able to do or struggles with due to PMS? Select TOP 3



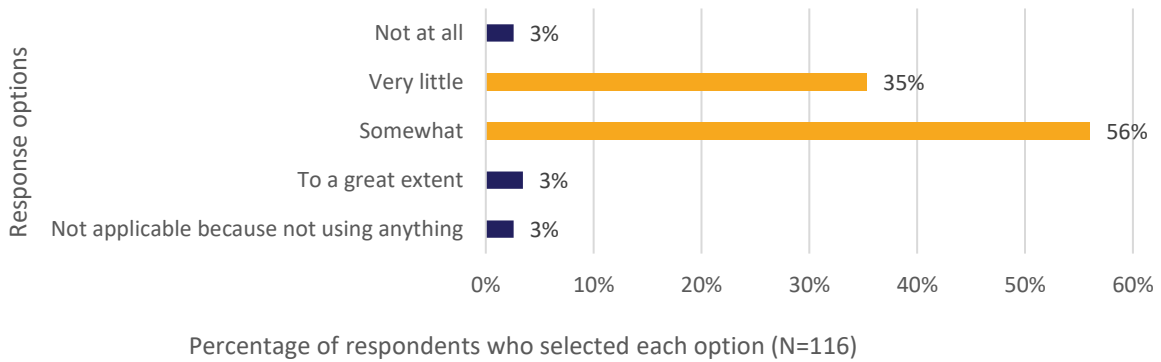
4. What worries you most about your loved one's condition in the future? Select TOP 3



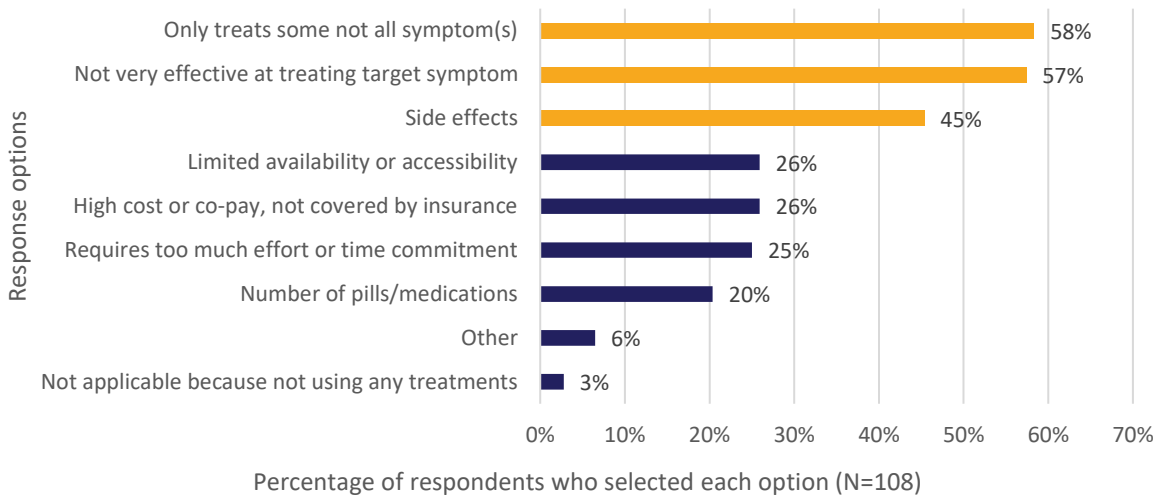
## Appendix 6: Session 2 Poll Results



### 3. How well does your current treatment regimen treat the most significant symptoms of PMS?



### 4. What are the biggest drawbacks of your loved one's current treatment approaches? Select TOP 3



### 5. Short of a complete cure, what specific things would you look for in an ideal treatment for PMS? Select TOP 3

