Additional Patient Comments from the Online Submission Portal

Phelan-McDermid Syndrome Externally Led Patient-Focused Drug Development Meeting

CureSHANK and the Phelan-McDermid Syndrome Foundation hosted an Externally-Led Patient Focused Drug Development (EL-PFDD) meeting on November 8, 2022. This EL-PFDD meeting was modeled after the work of the FDA's Patient-Focused Drug Development (PFDD) initiative, a systematic way of gathering patient and caregiver perspectives on their condition and on available treatments. The information gathered at the meeting is presented in the *Voice of the Patient* report, which may be used to guide therapeutic development and inform the FDA's benefit-risk evaluations when assessing therapies to address PMS. The report is publicly available for the many stakeholders in the LGMD community including the FDA, other federal agencies, academics, clinicians, advocacy and professional organizations, biopharmaceutical companies, and universities from across the world.

To ensure that as many voices as possible were heard, an online comment submission portal was open for one week before and four weeks after the PMS EL-PFDD meeting. Submitted comments are presented in this document, and caregivers are identified by their first name only. Some comments were edited slightly for spelling and punctuation. Selected comments are included in the main body of the *Voice of the Patient* report. The *Voice of the Patient* report is available online on both the PMSF and CureSHANK websites at pmsf.org and cureshank.org, respectively.

Mary L., mother of an 18-year-old living with PMS

Do all Phelan McDermid patients experience regression?

Julie and Gerard, grand parents of a child living with PMS (translated from French)

My granddaughter is affected by this disease. I want to participate.

Shelby, mother of a 49-year-old daughter living with PMS, diagnosed at the age of 42

The three symptoms that have had the most significant impact: neuropsychiatric episodes, regressions, loss of conversant speech.

The best day now is when she sleeps, has no stare spells, is able to interact in her environment and communicates.

Her worst day now is when she cannot sleep, yells and screams or seems totally out of it.

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. Early on when an episode started she would scream, "I'm getting sick. Make it stop! Make it stop." Right now she seems not to notice.

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. Ativan and then Klonopin have helped the most with anxiety, seizures and Catatonia. She hasD10 infusions two days a month and takes DepoProvera to shut down her cycle. Since that regimen started six years ago she has not been in patient in the hospital. She takes vitamin C, vitamin E, high gamma E, Vitamin D3, folic acid, Vitamin B complex, zinc, biotin, ubiquinol, carbidopa/levodopa, Carnitor, calcium, Linzess, Dulcolax, and Klonopin. Each has been added for a reason. Mary has had many diagnoses. She was diagnosed with Phelan McDermid Syndrome at age 42. She is now 49. Her 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. Twice in the last 7 years she has ceased to talk completely-no sound at all. Most times her speech now is non conversant. Neuropsychiatric episodes started at onset of puberty. When she was in middle school, after going many places to try to figure out what was wrong she said, "If they can't figure out what is wrong with me, can they study me and help someone else?"

Anna, mother of a seven-year-old daughter living with PMS

Our 7-year-old daughter, Lily has Phelan McDermid Syndrome caused by a de novo mutation in SHANK3. She was diagnosed in 2018 at age 3. Her first year of life seemed normal and then at 12 months old we began to see changes in her. She lost skills such as babbling, pointing and self-feeding with a utensil. She could not walk unsupported and socially she seemed to slip into her own world more and more. She did not walk until 20 months of age and only then with the assistance of orthotics to stabilize her low muscle tone.

She was diagnosed with Level 3 ASD at age 2 and then following an UTI with high fever at age 33 months, she suffered from a sudden and devastating loss of skills. Overnight she stopped playing with toys or her neurotypical twin brother. She no longer responded to calls of her name. She lost use of her right hand and almost all her fine motor skills. Her gait and leg coordination also changed drastically, and she suddenly could no longer climb stairs or use playground equipment. It was heartbreaking.

Lily is completely non-speaking but will use sounds to communicate joy, pain, or protest. She has been seeing a Speech Language Pathologist and Occupational Therapist regularly since she was 2 years old. 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.

Our sweet girl requires constant adult care during all waking hours. Her room is fitted with sound and video baby monitors so that we can respond as needed at night. She sleeps in a specialized seizure bed made of solid wood with four posters surrounded in strong netting that can be zipped up at night to prevent Lily from falling out of bed or getting up at night and harming herself through falls.

When my son (Lily's twin) was 4 years old, he once asked me why his sissy didn't play with him anymore. He wanted to know if it was because she didn't like him. My heart broke for him and broke for our family. We have all suffered so much loss from this disease. We cannot participate in "normal" activities because we have a very full schedule with therapies and medical appointments. Even if we can make it to a community event, my husband and I are stressed the entire time trying to keep Lily content and safe – all while watching the awkward glances from others around us.

I have had to learn how to navigate complex conversations with Lily's medical and therapy teams to manage her care. I am convinced that two of the greatest challenges we face in caring for Lily stem from her complex seizure disorder and the global hypotonia that strikes any given muscle group at any given time. She has lost and regained and lost skills countless times. No matter how hard we try to treat the symptoms with OT, PT, SLP and ABA – the root cause of a poorly functioning brain remains.

The only true hope that we have is something that can address the disease at the source.

Until then we will continue to fight to help Lily gain skills and improve her chances for independence, despite knowing full well that when the next wave comes, we could be back at ground zero again.

Kelley, mother of a 29-year-old son living with PMS

Comment 1: My child with PMS for years was treated with Rispardol, 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. At times our child would look at us and you could just read his eyes please stop this chaos this is causing in my brain. See our child is nonverbal very low functioning 3-5 years and he is 29yrs old. Psychotropic medications never worked well with our child. It was not until he was 27 when a new doctor suggested we ween him from medications and try Ativan. Although this is not an ideal medication it does help with mood however causes him to not sleep 4 out of 7 nights causing manic episodes and catatonia.

Comment 2: Somewhat things have been helpful such as ABA, Ativan and Lamictal our son lives in an ISL home with 24hour staff. Typically, a behavioral team responds as Kyle has aggressive

behaviors. A lot of it is related to the fact he is nonverbal and although he shows or tries to show what his wants are, if staff does not understand he will grab staffs shirt or pull hair. Also because of severe constipation he has severe pain in the belly.

Juan Fransisco (submitted in Spanish)

- La epilepsia es el peor sintoma, unido a los estados de no alimentación.
- La dificultad en la falta de comunicación con ella hace que todo se multiplique por mil.
- Hay mucha dependencia de ella con nosotros (total) y al revés, que no permite llevar una vida tranquila y social plena.
- Hemos probado muchas terapias y las que mejor le han ido han sido las acuáticas y con caballos.

Juan Fransisco (translated from Spanish)

- Epilepsy is the worst symptom, together with states of non-feeding.
- The difficulty in the lack of communication with her makes everything multiply by a thousand.
- There is a lot of dependence on her with us (total) and vice versa, which does not allow us to lead a calm and full social life.
- We have tried many therapies and the ones that have worked best for him have been aquatic and with horses.

Ricardo, father of a son living with PMS

My son Carlos has 22q13. Symptoms with most impact are:

- Non-verbal
- Global Developmental Delay
- Sleep disturbances

Cathy, mother of a 41-year-old son living with PMS

Comment 1: Christopher is 41. Finally diagnosed at 29.

He was fairly independent. He would wake with an alarm clock, get himself ready for school/program, watch to clock for the time for his ride, get up and exit the house to wait. Arrive home independently, let himself in, get a snack, let the dog out. Eat and shower independently. He voted, received the religious sacraments. Went on a date. Traveled with his special Olympics team. He rooted for his sports teams and against his brothers (as any typical sibling would). He read, wrote at a basic level. His verbal skills were great!

Today, he needs assistance waking, dressing, showering, eating. Is doubling incontinent. He is constantly in motion. Doesn't enjoy one single thing in his life! His eyes are empty. He doesn't smile and he doesn't laugh.

We are just outside of NYC and there is limited medical resources. The neurologist that is willing to take on a rare syndrome doesn't know what more to try. There are no other options open to us. And again, we are in a densely populated [urban] area, not a rural area.

How do we as parents proceed? How do we as aging parents proceed? The number of adults identified with PMS is small, is this indicative of their future?

Comment 2: We are the parents of an older PMS child. He's 41. It's frightening to think about the little amount of time available to us to help him.

Over the past years, he progressed from being fairly independent to needing complete care. Along with this my husband and I have aged along side him. This syndrome takes its toll on the caregivers.

Christopher has moved to a great group home but it is another layer (sometimes a help) but also hindrance to help him since they have their own policies.

Talya, mother of a seven-year-old son living with PMS

I wanted to submit a comment highlighting an example of the secondary impacts of PMS.

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.

The reasons for this can be directly tied to his PMS symptoms:

(1) 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.

(2) He recently went through a period of severe anxiety with self-injurious behaviors, and part of our compromise to keep him from punching himself the face all night in bed was to allow him to eat snacks in bed. This of course led to the development of cavities, not helped by our inability to clean his teeth well (which was even harder during that time). Until we found medication that began to help his anxiety, it was pointless to even attempt a dental appointment. By the time he was improving, the cavities had formed.

(3) Once we determined that he would need fillings, it took more than three months to coordinate schedules of the dentist and the anesthesiologist (for the sedation), during which time several more cavities developed, despite our efforts to prevent them with fluoride treatments and antibacterial toothpaste. There was no way to get him into a sedated dental appt any sooner in Houston, the 4th largest city in the country--I called around! So the need for

sedated dental work made it take far longer for us to address his cavities than it would have for a typical child, meaning more cavities to fill--and more work for the doctors and a higher bill for us.

(4) The anesthesiologist informed us that he had to use THREE TIMES the typical amount of medication to sedate our son and that he came out of the sedation extremely quickly. This is likely related both to his PMS and to the fact that he takes to many medications already.

I wanted to share all of this because our son's dental health has become a major challenge--and expensive one--even though there is nothing actually *wrong* with his teeth. It is the symptoms of PMS that create this situation.

Sabine, mother of a 16-year-old son living with PMS

Comment 1: The biggest problem is: the hypotonia and the lack of language; Muscle Wellness and Lack of speech; Incontinence.

Comment 2: Since our son can't walk or crawl it is very tiring every day. He is completely bound to the wheelchair. Our son will soon be 17 years old. He is physically and mentally disabled. He cannot eat or drink on his own, and is completely dependent on our assistance. He has no speech. He requires diapers due to his complete incontinence. His size and weight make everyday life extremely difficult for us, especially with care and all the activities we want to do with him. On good days he is cheerful and helps out to the best of his ability. On bad days he is very grumpy and loud.

There are many activities that we cannot do with him because of his disability. Due to the fact that he cannot walk and he shows little interest in everyday things, many everyday trips are a challenge. Especially trips on vacation. Even normal visits to friends are usually not possible. For us parents it means that we had to limit many social contacts extremely. Our life is very much related to him. Because he only meets children or teenagers at school due to his disability, we find this very sad especially for him.

Our son had to struggle a lot. He was not able to hold his head on his own until he was almost 2 years old because his upper body was extremely hypotonic. He was at a different therapy every day, especially as a baby into toddlerhood, sometimes several times a day. Even today, therapies define his week. He enjoys most of them and loves being there.

Therapies are still to this day:
Physiotherapy, occupational therapy, speech therapy, osteopathy, riding therapy.

At school he has many aids to strengthen his muscles additionally: Standing device, running device, therapy bike.

We also tried dolphin assisted therapy on Curacao.

Muscle building is the most important thing for him, because of course we always hoped that he would learn to stand or walk a few steps after all. Unfortunately, he was diagnosed with hip dysplasia and hip dislocation in 2022. The doctors mentioned that it was due to sitting in a wheelchair. We have always tried a lot of therapies and have put him through a lot of therapies to get as much out of him as possible at a young age.
Now, at almost 17, he is still willing to learn, but, for us, and the therapists, physically just extremely exhausting.
For us, a medication that affects the muscles would have been a blessing.
Translated with www.DeepL.com/Translator (free version)

Dominique, mother of an eight-year-old son living with PMS

Our son is eight years old and was diagnosed with PMS at the age of three. He suffers from massive sleep disorder, mental delay and disorder of speech development. We have found ways to communicate with him, but what impacts our entire family most, physically AND mentally, is his sleep disorder. Every night he awakes minimum 5 times and often can't fall asleep for up to 3 hours. He can't sleep alone and so he makes our nights to days. No therapy works. And like him, we as his night buddies, are always tired and sick. We have no help from family or professionals. We have cut down on our hobbies, our social and evening activities, to go to bed as early as possible. It's tremendously tough!

Gail, mother of a daughter who passed away from PMS complications

Joanna's most difficult symptoms were:

* Chronic 'tummy' pain. Joanna often looked sad and in pain. As best we could work out, having eliminated as much as we could with ultrasounds and X-rays, this was related to her stomach. Perhaps/ most probably it seemed to be related to her bowels. Jo needed constant vigilance with her bowels in her adult years - chronic constipation.

* Agitation/ sleeplessness/ mania like behaviours. Sometimes aggressive.

Joanna needed constant monitoring. In her adult years, Jo needed someone with her all the time. She 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. On her best day Joanna enjoyed reading kids books, craft, chatting, sharing a joke. Always at her simple level. Always with a companion.

Our whole lives were completely affected by PMS. Our family activities always needed an easy 'exit plan'. And we only ever considered family activities we could confidently attend with Jo.

Over time Joanna's symptoms increased and became more difficult. Joanna required psychiatric medications for anxiety, and difficult behaviours. Joanna's last years were in a house on her own because of difficult behaviours - screaming, awake all night, etc. She needed staff awake all night and two staff for outside activities. Joanna passed away in January 2021. Her Death Certificate registers complications of PMS. It was completely sudden, and we have all the hospital notes from her final hours.

Joanna only used medication after the age of 17. This was for difficult behaviours. Medication was a constant roller coaster. Symptoms were never completely addressed.

Albert and Valentina, parents of an eight-year-old son living with PMS

Comment 1: We are submitting this long version of our report for the Voice of the Patient report. We will submit a shorter version that's more digestible as well.

Our eight year old son Joshua was diagnosed with autism just before he turned two. After that diagnosis, we did genetic testing, the first round of which showed nothing. We then took him to a geneticist specializing in autism. She agreed to test Josh using whole genome sequencing, but assured us that we'd likely find nothing since he didn't show typical symptoms of someone with a genetic condition. Lo and behold, Josh came back with a positive diagnosis for Phelan-McDermid Syndrome just before he turned four. A renowned geneticist didn't think he'd test positive only four years ago, which tells us just how under-studied our condition is.

Having the PMS diagnosis didn't give us treatment options but it did connect us with other PMS families and allowed to watch out for warning signs. And there are MANY possible symptoms to be aware of, from seizures to psychiatric changes in the teenage years.

For us, the main ways Josh and our family are affected include:

-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.

-It's also hard to say how much Josh understands. We think he understands more than we realize, but then we see him struggle

to understand that taking his pants "off" doesn't mean to pull them back up.

-He can't take care of himself. This includes not being able to dress himself, shower himself, brush his teeth or use the bathroom on his own.

-We have tried many ways of potty training and, while he has certainly improved over the years, he still uses a suppository for BMs and wears a pull-up at night. We keep a spreadsheet and fill out a row each time Josh uses the bathroom. We know to take him every 60-90 minutes or so, to avoid accidents. Otherwise, he will wet himself. When Josh goes to the bathroom, one

of us (or a therapist) will always go with him, to make sure he actually goes, and also to help pull up his pants, wash his hands and dry his hands.

Sometimes, if he has a BM accident, he will put his hand in his butt and smear the feces all over our walls (and sometimes his body). I apologize for being graphic but that's our reality.

-Josh doesn't know what to do with his free time when he's not occupied with something structured. Josh has school from 8-3 and then he has another two hours of private ABA-based therapy at home. So he has 9 hours a day of instruction. When he doesn't have this structured therapy, he doesn't know how to occupy his down time. He will ask on his AAC to watch tv or listen to music (he likes specific songs or shows). Those are his main leisurely activities and we so wish there were other forms of self-entertaining he could do.

-Josh has a lot of sensory issues. When he gets more sensory input (eg 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.

-While Josh is probably a better sleeper than other PMS kids, sleep is definitely an issue. He will usually fall asleep within 30 minutes but will sometimes jump around for 90 minutes before falling asleep. His average sleep is 9-5 or maybe 9-5:30, but there are many nights when he'll wake up at 1 or 3 and will need one of us to lie with him for an hour or two to fall back asleep. And other nights, he'll be up at 4 for good.

-Another issue is his GI. Like many other PMS kids, Josh has a very sensitive stomach, though he doesn't typically have constipation (besides one incident I'll describe shortly). He will have a loose stool or diarrhea if he eats something not settling with him, so we keep him gluten and dairy free and limit his grains, sugars and fruit. We also make him a large pot of chicken soup every single week and he has a glass of the soup daily. There was one incident two years ago where we allowed him to have two slices of pizza, and he didn't have a normal BM for 9 days after. We had to take him to the hospital and give him several enemas, plus various forms of medication. Needless to say, he hasn't had much pizza since then.

-He mouthes 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.

-Another area where we struggle is the balance of therapy approaches. Many people in our community are against ABA therapy and discreet trials (repetition of tasks in order to remember behaviors or skills). Higher functioning autistic adults often speak to how much they hate ABA and prefer other, more open approaches. While we do think that more open approaches have their place (for example, we think letting Josh have his AAC device at all times and allowing him to use it at will rather than forcing him to repeat phrases is the best approach for teaching communication), we can't live without the ABA. We have recently tried the Floortime approach where they follow Josh's lead, but in truth we haven't seen a ton of

progress there. We are lucky that our private ABA team doesn't come at it with a very rigorous style and they're very open to working with Josh at his pace, but we often struggle with finding the right balance between ABA and other approaches.

-We've written a lot here, but really our biggest fear is what happens after we parents die. Josh has a younger 6 year old brother, Ben, who loves him so much. He keeps asking us when Josh will talk and that he wants to be able to talk and play with him. It breaks our heart that he can't play with his brother and it also breaks our heart to think that he's Josh's only sibling. We don't want Ben to think that he has to take care of his brother when their parents leave this earth, but we realize it's something he may want to do anyway.

-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.

If there's some magic pill or therapy that helps him communicate better (whether or not he talks, just communicating more on his AAC device would be amazing), that would be the other dream.

We know these may be difficult to achieve but we can still dream. Regardless, Josh is a happy boy and his smile lights up a room. This is in spite of him having to work more than almost any child his age, to make up for what doesn't come to him naturally.

All us parents just want our kids to be happy, and Josh is, for the most part, happy. But a small part of us still holds out hope that maybe, with some help from medicine and science, he will be able to progress a little more one day that what we've used to expect and have had to accept.

Thanks, Albert and Valentina Klyachko

Comment 2: We feel your pain about deciding whether to take both our kids (one PMS, one neurotypical) to sporting events, shows, etc. We struggle with this all the time!

Comment 3: I had to jump early but thank you so much for organizing this fantastic event. I learned a lot from the sessions and have already reached out to several parents in regard to some tactics they spoke about as working for their kids.

This was super informative and so many of the shared stories were extremely relatable by us parents. Thank you again!

Comment 4: During the conference call, a lot of parents mentioned GI issues with their kids, and several parents mentioned reflux issues in young kids. So we wanted to add this comment about what has worked for us in terms of diet.

Like many other PMS kids, Josh (8 years old today) has a very sensitive stomach, though he doesn't typically have constipation (besides one incident I'll describe shortly).

Josh had reflux since he was a newborn and only when we first eliminated dairy did we start seeing a big difference. We did also eliminate gluten near that point as well. I'm not sure if gluten was a major issue, but eliminating dairy was the big reason for the help with the reflux.

At the same time, we also mostly eliminated processed sugar. We eventually even limited most fruit because of the sugar as well. (He still has bananas, apples and sometimes blueberries or raspberries.) We're not sure if removing the gluten itself is what helped, or if it was eliminating most grains altogether. 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.

We also did a series of food allergy tests. It showed only a mild sensitivity to gluten but showed strong sensitivity against foods such as dairy, rice and chickpeas. So we continue to fully eliminate those foods.

These days, he will still have a loose stool or diarrhea if he eats something not settling with him, so we keep him gluten and dairy free and limit his grains, sugars and fruit, along with other foods that showed to be sensitive for his gut. (We're currently trying to test if adding a little bit of gluten affects him, so TBD on that).

We also make him a large pot of chicken bone broth every single week and he has a cup of the broth daily. From what we've observed, there may be healing properties for the gut from the bone marrow when you slow cook it.

There was one incident two years ago where we allowed him to have two slices of pizza, and he didn't have a normal bowel movement for 9 days immediately after that. After a week of mostly diarrhea we realized it was time to take him to the ER and insisted on an X-ray. There was a blockage and only fluid was coming out around his BMs. We had to give him several enemas, plus various forms of medication. Needless to say, he hasn't had much pizza since then (though he had half a slice a month ago and was fine, so I think some of this has to do with only allowing certain foods in moderation).

To summarize, removing dairy from Josh's diet helped eliminate his reflux. Removing most grains, gluten and sugar seems to have helped us well. We are testing if adding small amounts of gluten will have a negative impact or not.

Happy thanksgiving everyone!

Comment 5: I wanted to add a comment about Pica since we just went through a scary experience with our 8-year-old son Josh.

We took Josh to the ER last night (Monday night) because he's been sick. We thought he had a stomach virus since he threw up Friday night three times and had diarrhea several times, and

then was having very loose stools after that. He seemed better Sunday and most of his appetite came back. Yesterday we sent him to school but his appetite was mediocre.

Last night, he had diarrhea again (watery and possibly with some mucus), and we brought him to the ER. He hasn't had a fever and has been in mostly good spirits throughout.

The x-ray last night showed that he had some obstruction in the upper part of his stomach and they think it was blocking food from getting to the colon. We think that the obstruction is caused by the paper Josh has been chewing (and swallowing). He likes to tear pages from his books and chew on them. But apparently he'd been swallowing more than we have realized. So this is typical behavior of Pica.

They were recommending surgery to remove the obstruction. They thought it was a bezoar due to pica.

Luckily, the enema they gave him last night seemed to help, and he had a large bowel movement this morning.

While the X-ray last night looked quite bad, the CT scan he had this morning looked much better, and hopefully he'll be able to go home today.

We will now have to not let Josh have access to books when he's alone, so he can't have access to the paper. I know many other kids with PMS have Pica issues, so adding this experience for that reason**.**

Sandra, mother of a 24-year-old daughter living with PMS

Comment 1: As a mother of a 24-year-old PMD girl, I would like to submit the following comments on my experience of the PMD syndrome.

For me one of the biggest challenges of the PMDS is having to deal with contrasting cycles:

- cycles of passive and apathic mood/behaviour;

- cycles of agitated and hyperactive mood/behaviour;

These "low" and "high" cycles can be observed over long periods (sometimes seasonal) and short periods (during one day).

During the "high" hyperactive cycles, very often sleep problems are also observed.

These cycles start during childhood, but it is during adolescence that they become extreme and particularly challenging. Hormonal changes exacerbate the cycles. Serious sleep problems often start at this age during the "high" hyperactive cycles. Suddenly PMD individuals can resist sleeping for several days in a row - that is extremely difficult for them and the parents.

The need for medication for my loved one started clearly at adolescence. The contraceptive pill was the first medication introduced with the objective to stabilize the hormonal ups and downs.

She has been on the pill (Cerazette) since age 16 and it has made her gain weight year by year. She is otherwise doing well and we are afraid of endangering this fragile equilibrium by stopping the pill. I wish there was an alternative medication to stabilize the hormonal unbalances without this slow and constant weight gain.

Another treatment which we use in times of strong agitation is Risperdal. As the behavioural changes appear suddenly, this treatment is generally introduced as emergency intervention. Once it is started, it becomes very difficult to withdraw and has to be stopped very gradually and slowly. As this medication also has side effects (weight gain among others), it is very frustrating to have to continue for long periods of time once it is introduced.

I would also like to mention that at adolescence my child started suffering from hypothyroidism and ever since she has a specific treatment for this pathology (Euthyrox).

Finally, I would like to add that one of the most significant aspects of the PMD condition is the incapacity or general difficulty to concentrate, especially for longer periods of time. Since two years, we have introduced a zinc treatment which has helped her concentration and general well-being.

Comment 2: My daughter, 24-years-old, also experienced regression during puberty, following psychiatric issues.

I wasn't able to click "regression", because I had already clicked all the previous options (except for seizures). However, the potential of regression is something we worry very much about for the future.

Having experienced regression in the past, we try to keep a stable environment as much as possible to minimise the risk of reoccurrence.

Comment 3: Social isolation which may increase with age is a big worry for us. This is even more true considering that my daughter has a very hard time occupying herself and needs to be stimulated and accompanied constantly. She depends on others and at the same time loves to be around people. She hates to be by herself and follows me everywhere in the house**.**

Comment 4: I find 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 Risperidone.

Today she is still on the pill and the problem is that it makes her gain weight, but I am too afraid to stop it.

Bernadette, mother of a 33-year-old son living with PMS (submitted in French)

Mon fils a 33 ans . Les symptômes les plus significatifs chez lui = déficience intellectuelle , langage très restreint et troubles du comportement .

Dans les meilleurs jours il est calme , coopérant , arrive à se faire comprendre ,dans les mauvais jours c'est de l'agitation , opposition , impossible de le comprendre , aggravé par de l' incontinence urinaire .

Il est impossible de l' emmener dans un magasin , veut tout acheter, les repas sont compliqués car boulimique et précipité .

Dans l'enfance ses symptomes majeurs étaient la déficience intellectuelle , les troubles du langage et les difficultés d'organisation du mouvement. A l'âge de 20 ans sont apparus des troubles du comportement avec des colères , crises d' opposition et crises clastiques

Puis une régression globale de ses capacités intellectuelles et langagières avec perte d'autonomie et incontinence urinaire .Il a maintenant 33 ans .

Il prend un traitement médicamenteux par neuroleptiques (dont un grand nombre qu' il ne métabolise pas), sédatifs et antidépresseurs et a besoin d' un accompagnement individuel permanent pour la vie quotidienne. La gestion du quotidien reste difficile et épuisante pour la famille comme pour les éducateurs

Bernadette, mother of a 33-year-old son living with PMS (translated from French)

My son is 33 years old. The most significant symptoms for him include intellectual disability, very restricted language and behavioral problems.

On the best days he is calm, cooperative, manages to make himself understood, on the bad days it is agitation, opposition, impossible to understand, aggravated by urinary incontinence.

It is impossible to take him to a store, wants to buy everything, the meals are complicated because he is bulimic and hasty.

In childhood his major symptoms were intellectual disability, language disorders and difficulties in organizing movement. At the age of 20, behavioral problems appeared with tantrums, opposition crises and clastic crises.

Then a global regression of his intellectual and linguistic abilities with loss of autonomy and urinary incontinence. He is now 33 years old.

He takes medication with neuroleptics (many of which he does not metabolize), sedatives and antidepressants and needs ongoing individual support for daily life. Daily management remains difficult and exhausting for the family as well as for the educators.

Diana, caregiver/family member of an individual living with PMS

- Uncontrolled seizures

- Low muscle tone
- Intellectually disabled
- Globally delayed
- Cerebral palsy make it really impaired our whole family

Jessica, mother of a seven-year-old son living with PMS

Mentally roman is unaware of anything he is like a 9-month-old baby in a 7-year-olds body. So the intellectual disability, development and speech delay, autism would be the main 3 of Romans life.

This means he will have to live with me his whole life he will never be able to live a life without 24/7 care. This has changed my whole life. I've had to give up everything in my life, career, lost friends, mentally. All to look after my son, which I will never stop doing.

Roman actually hit all his milestones and progressed as a normal child until he hit 2.5 years and he started to regress with his speech, they assumed autism but then a blood test flagged PMS. I couldn't believe it.

Since his diagnosis all his done is regress and lose his abilities, which is the saddest thing for me to swallow as he used to play with toys, use a cup etc and now he just can't do any of the things he used to, and I have no explanation why.

Going on holiday for us is impossible. Roman gets motion sickness for one, he is very dependant on equipment we have in the house for his feeding, sleeping so going on holiday just isn't an option for us which makes me sad.

Roman is extremely sensory. He mouths everything and anything, this started in 2019 when he became poorly with low blood sugars since then all he has done and wants to do is chew! He explores the world with his mouth and through touch, which can be dangerous at times if he mouths things inedible. We manage through having routine and we don't have many places that are "roman safe" that we can go too other than our house and his school.

Which is very isolating, for us all as a family. Roman also has ADHD, we haven't currently found a medication that's suits him after 3 years, he is so sensitive to symptoms and as he can't communicate with us, we are constantly guessing how he is reacting to meds and if he does have any symptoms!

Inez, mother of a four-year-old daughter living with PMS (8.7 mb deletion)

Of all the symptoms of Phelan-McDermid syndrome, which 1-3 symptoms have the most significant impact on you or your loved one's life?

Ivy-Rose (4years old) was diagnosed at 8 months, is heavily affected by PMS with a deletion size of 8.7mb she is left blind, non-verbal, non mobile, tube fed, with epilepsy, wheelchair dependent, lymphoedema, gastro problems, sleep issues, dystonia, and more.

Ivy-Rose requires 24hr care, needs assistance from adults and equipment all day and night, including a specialist wheelchair, a supportive postural chair, a supportive comfortable chair, a standing frame, hoists, an indoor lift, an accessible shower room, a sleep system, AFO's and more.

Of all of the PMS symptoms I would say the 3 hardest for Ivy-Rose are-

1.) Her gastro problems, although we have not found the exact cause for the vomiting that happens anywhere between 15-30 times a day. We have tried every single available reflux medication, removing things from her diet, slower feeds, less feed, we have tried so many things yet so far are still in the dark. The constant vomiting results in her having to have showers several times a day and clean clothes, bibs, muslin cloths etc. It is debilitating. She often vomits up bright yellow bile acid even with a full stomach. Ivy-Rose has an unsafe swallow so is tube fed for all of her nutrition.

2.) Constipation/inconsistent bowels. Ivy-Rose suffers terribly with constipation. She will often go days without opening her bowels, and then have days where she is really struggling to go, and when she eventually does it often causes seizures as it is so hard for her. She is on daily laxatives which do not consistently help her.

3.) her epilepsy (although currently well managed with medication) that caused Ivy-Rose to lose her vision at 18 months due to going into status epilepticus (ongoing seizures) for 12 days resulting in a 6 week hospital stay, medical lines drilled into the bone marrow of her legs and being put into life support.

Stefanie, mother of a three-and-a-half-year-old son living with PMS

Of all the symptoms of Phelan-McDermid syndrome, which 1-3 symptoms have the most significant impact on you or your loved one's life?

The biggest symptoms of PMS impacting our lives currently for my son Freddie are GDD (global developmental delay) especially gross motor delay due to severe hypotonia. He also had hip dysplasia when born and wore a Pavlik harness for 3.5 months which also delayed his ability to build muscle strength. Freddie is 3 and a half but is not mobile. It took him around 12 months to improve from sitting unaided for 20 seconds to be able to do this unlimited. I am carrying him everywhere and this affects me physically as well as not safe for him it means we need full disabled access and facilities wherever we go. He is relying on me to bring the world to him and I pray he will walk one day. This also means being unable to take part in lots of typical kid activities meaning it's hard to keep him stimulated outside of nursery time. It also means he is fully reliant on me to entertain him every second of the day as he does not play by himself yet due to his delayed fine motor skills.

The other biggie is the absent speech. Especially when other symptoms include high pain threshold and not regulating body temperature for Freddie to not be able to voice these incidences to me could be very dangerous or fatal. For example he had a slight temperature

recently which turned out to be scarlet fever and led to him having two seizures but I did not know how poorly he felt as he's had temperatures before and there were no other symptoms from the fever at the stage of having the seizures (body rash , puffy tongue etc) had I known how poorly Freddie felt I could have better prepared for the escalation or have kept him from over heating.

How does Phelan-McDermid syndrome affect you or your loved one on best and on worst days? Describe your best days and your worst days.

My worst days are when Freddie is unwell and I have no idea what is wrong with him. To feel poorly and not always have all needs met or not as soon as they could be if he could communicate this to me is both heartbreaking and unfair. We have to have doctors appointments or hospital appointments until we get to the bottom of it. Freddie is usually upset for good reason as I am lucky that he's generally a very calm loving happy boy but on days when he's unhappy and I don't know why he can cry most of the day which has an emotional toll for everyone.

The best days we have are when we can get out and about but this is during warmer months and over winter it's a lot harder to keep Freddie stimulated and happy as the weather makes it harder to go outdoors. As Freddie cannot play independently yet as he does not have the fine motor skills to manipulate toys our best days are days when we go for nice walks and to the park or farm or for a picnic outdoors where he can see the birds and the clouds and people watch. He absolutely love books so reading lots of stories outdoors especially is his favourite thing. We also go swimming where There are accessible changing areas and get help from the leisure centre staff with getting him in and out of the pool.

Are there specific activities that are important that you or your loved one cannot do at all or as fully as you would like because of Phelan-McDermid syndrome?

Typical children's activities like playing at the park if there aren't inclusive equipment. Soft play centres for indoor fun. Children's parties where there are certain party games, ride on toys, baking and crafts. Typical family activities like bowling or the cinema, theme parks rides etc

How has your loved one's ability to cope with the symptoms changed over time?

Freddie has definitely improved with coping as he used to get very frustrated and shout out or get upset and he went through a stage of also trying to shuffle himself when on the floor unaided as if trying to move to reach something but he's since found ways to express some wants to me by guiding my hand or gazing at something that he wants or reaching in the direction so this has helped his coping mechanisms.

What are you currently doing to manage your loved one's PMS symptoms?

Freddie has a physio and occupational therapist as well as a specialist PNI teacher and we have had a social care referral for adaption assessment at the house. We also have a speech

therapist and I have learnt basic makaton [sign language] and have regular meetings with the nursery to discuss his objectives and goals. I've also requested and been granted an EHCP for when he starts school next sept 2023 to get him all of the help he needs. We also have a blue badge for disabled parking to help with getting out and about and a motability car on order to also help with this and to get his specialist pram and equipment from a to b. We have a few different types of equipment and aids supplied by the NHS

How well do these treatments address the most significant symptoms and health effects of PMS?

The above health professionals and their programmes help with most aspects of the condition. The physio programme helps with the muscle strengthening Freddie's needs in order to develop his gross motor skills, his walker supplied by the NHS via his physiotherapist for example helps with his weight bearing and core strength. Physio would be the area where I feel the treatments / sessions are the most important and regular. Luckily Freddie doesn't have any cardio or kidney problems and no major issues with swallowing due to low tone he can handle most foods with lots of fluid. Luckily there's no signs as yet of him developing seizures as those are a big health symptom of the condition.

Brad, father of a 24-year-old son living with both PMS and Lennox-Gastaut syndrome

Impacts on daily life: 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. For this reason, he has someone within arm's reach 24-7. We are constantly trying to balance safety and autonomy – keeping him safe while giving him some freedom to explore his environment and to "communicate" through his actions.

Treatment failures: 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. -

Megan, mother of an adult daughter living with PMS

Comment 1:Of all the symptoms of Phelan-McDermid syndrome, which 1-3 symptoms have the most significant impact on you or your loved one's life?

1. Catatonia
2. Anxiety
3. GI issues/pain

Best day, my adult daughter is energetic and engaged with others.

Worst day, my adult daughter is catatonic, anxious, has lost critical skills (gross, fine, oral motor) and does not engage with anyone.

She does not sit down unless she is eating or on a toilet. This means anywhere we go she needs to be standing and moving. This makes non-car travel, movies/ /shows, attending and adult day program, and most family events impossible.

Comment 2: QoL - Comment about the need for therapies (NOT a argument abut the US health system ;).

COVID taught us how CRITICAL maximum therapies received through the school system was. Once she was out of school for COVID she became very tight 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).

Comment 3: NEED for Dedicated Physician to manage meds:

Beginning at age 14 our daughter began having psychiatric regression and catatonia. She has had 6 crises in 6 years. Each time the "red flags" present in different order with varying severity (getting worse with age). Each crisis requires an increases/decreases in medications (Lithium, Ativan, Depakote, Gabapentin) If a family doesn't have a VERY open minded and skilled psychiatrist or neurologist to manage these medications things may get worse with the use of the wrong medications and permanent loss of skills (described by an earlier caller).

Comment 4: Future Treatment wish -- prevention of psychiatric regression and catatonia (which is likely much more common across all NDDS / ASD than the medical community recognizes).

Heidi, mother of a 19-year-old son living with PMS

Our son, Hayden, is 19 and has had almost every symptom. Communication deficits, severe intellectual disability and catatonia are the most debilitating for him.

This affects all of his day and ability to be independent. One parent, me, had to shift careers and quit all together as he requires 24-hour care. On his best days he can enjoy (or we think) activities but still needs help with all ADLs and is now tube fed (new in March of 2022). On his worst day ever it can involve the hospital, doctors unable to help due to lack of knowledge and us having to tell his life story over and over to every new person. It is exhausting. Due to no standards to treat/diagnose, my son was diagnosed at almost 18 in 2020. This also caused delay of treatment and mistreatment that harmed him further.

His ability to cope with symptoms is not good these days. He has regressed and is now on hospice as they feel it will persist and will not go away (catatonia). If he would have had proper treatment this may not be the case.

My son is on Ativan, lithium, tube ged formula for nutrition and 2x a week ECT treatments. It is these three things giving him quality of life. He is on 18 mg of Ativan daily, which most shake their head at, but it helps him so much and makes perfect sense. Without these treatments I believe our son would not be with us and we already know it is limited. Thank you for your time and consideration. Hayden and his de novo genetic condition matter!!

Liz, mother of a son living with PMS

Comment 1: three symptoms that have the most impact on Mason's life

1- Communication -expressive/receptive impacts his life globally

2-Fine and gross motor skills - impacts activity of daily living and vocational opportunities

3-Sleep

Comment 2: Activities we cannot do - 1) travel. Hard to even travel with Mason. We go places that are reachable by car and stay in vacation rentals. We have to remain vigilant because Mason has a history of elopement. We do travel but not often. 2) 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. 3)Finding quality home heath care has always been and continues to be challenging.

Comment 3: As Mason has gotten older his activity level has decreased and weight has increased. Motor skills make activities difficult.

Comment 4: Listening to the first mom talk about feeding, rash, falls... I could read her story and just change Hudson’s name to Mason. We are you.

Mary S., mother of a daughter living with PMS

1. Sleeping disorder.

Kerri can be very, very loud.

Inability for self care, toileting, dressing, eating....

2.Worst days: sleep disorder combined with mania where she takes everything out of everywhere...for days!

Best days when she laughs and giggles and has fun. When we see peaks of her...making jokes accomplishing stuff as "normal".

3. Everything. Kerri cannot be left unattended!

4. She has simply stopped trying to do most things. She will tell you "I can't do it " without even trying

5. CBDs, Xanax, weighted blanket, pot brownies, for sleep. My husband and I take turns at night getting up with her.

6. Maybe 25% helpful. Sleep deprivation sucks!

Laura, mother of a 22-year-old son living with PMS

Comment 1: The symptoms that have caused my son the most stress have been:

1. Sleep - My son falls asleep normally, but wakes typically between 2-3am and often will not sleep more, and 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.

2. 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.

3. My son also has struggled since age 14 with manic cycles, originally treated with Abilify, which caused increased rage and aggression, as well as causing a significant increase in daily seizures. We have since tried many antipsychotics, some causing serious catatonic episodes that could have been life threatening. He is currently on Ativan and a very small dose of Lithium and is the most stable he has been for over 6 years. But the frequent uncontrolled mania, resulted in several month-long hospital stays, weeks in the emergency room in a very frightening and difficult environment.

As my son has gotten older, he is now 22, 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.

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.

My son has spent many years in various therapies, ABA, Speech, OT, PT, Hippotherapy, water therapy, alternative communication strategies, and while some of these have helped him, he often loses the gains he makes once the therapy is stopped.

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.

I have concerns over the future as my son's health seems to decline a little every year, and yet he is just barely an adult, so we have to wonder what comes next, and try our best to prepare for what may come.

Comment 2: 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. ADA 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).

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.

Comment 3: 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. Constipation medications do not solve the problem but are more a band-aid. Botox works a little but wears off quickly and requires minor surgery several times per year. Being unable to use the toilet independently at 22 years of age really impacts his everyday life.

Sarah, mother of a daughter living with PMS

Here is a write up of what it is like for us each day as we care for our daughter, Isla. I have listed as best I can, all ADLs she requires support or assistance to complete and arranged them in chronological order from the moment she wakes up, until she goes to bed each day. I have also included recent examples of dangerous situations and emergencies we have endured, some of which required medical care, due to Isla's lack of safety awareness, behaviors that have caused self-harm and also threatened the well-being of those of us living with her. We hope this gives you a clear picture of the challenges and level of care our daughter requires day in and day out.

Isla wakes up every day around 7:30am. She cannot get out of bed without full assistance. She is approximately 45lbs and does not assist us in getting her into or out of any of her equipment, including her bed. She must be carried and lifted onto her changing table where we have to change her diaper as she is completely incontinent. Diaper changes often require two people to manage since she constantly and aggressively attempts to kick, roll, stick her hands

into undesirable places and substances, sit up, grab anything within reach and occasionally bite. She has also toppled herself off of the changing table on more than one occasion as we turned to reach for something, or she suddenly lunged, unaware of the danger of falling. She often requires treatment for rashes or sores due to wearing a diaper and exposure to her urine or fecal matter. She recently suffered from what we think may have been a yeast infection that was so bad we had to give her baking soda baths twice daily and apply anti fungal cream for 2 weeks before it began to heal.

Isla cannot do anything to dress herself. 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. She requires a Spio suit for trunk support and AFOs for ankle support when standing or taking steps with full assistance. The Spio suit is tight and difficult to adorn and between that and her AFOs, this adds a considerable amount of time and effort (more than double the time it takes to dress her 3-year-old sister). If Isla has had one of her frequent blowouts, she receives a bath before she can be dressed, another difficult task for which she is completely dependent and actively unhelpful in receiving. More details on that in her bedtime routine... Isla must then be carried down the stairs to the dining room for breakfast. She is tall and heavy and if she is not feeling cooperative, she endangers herself and her caregivers as she will sometimes buck and lean away from the person carrying her. This not only causes her to bonk into walls and rails, but endangers herself and the person carrying her to potentially fall down the stairs. My husband has fallen twice while carrying her.

Once downstairs, Isla must be placed into her activity chair (a special chair with added trunk support and a tray she requires since she has outgrown any infant highchairs and requires the added supports for her hypotonia). She requires a bib since she often drools and spits food out, and regularly chokes and vomits. She also chews her hands incessantly between bites, getting bits of food everywhere and staining all her clothes. She requires constant supervision while we ready her breakfast, since she can rock her chair or use her hands to move herself toward objects she should not reach. She frequently tips chairs over, has pulled decorative objects and cutlery or ceramic plates and bowls off of tables and shelves and if she can remove her bib or get access to the extra hanging bibs, she will chew it and is at risk for breaking off pieces of the plastic. 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. Isla cannot use a spoon or fork and must be fed anything that cannot be placed on her tray. Isla has chewed through countless sippy cup lids and straws and must be watched constantly to make sure she is drinking from her cup safely and not in danger of ruining or swallowing plastic parts she has chewed off.

Isla is not malicious, but does not know better and will also bite us when we use our hands to put food (or remove unwanted items) in or out of her mouth. More than once, she has injured her little sister who lovingly attempted to feed her bits of pretzels or veggie straws and got bit hard by an over eager and stimming Isla. Isla also has a dairy intolerance (but no awareness or understanding of dietary restrictions) and must be carefully monitored as to what she is given to eat. She has no understanding or awareness of heat and has burned herself on food that was too hot if we were not testing her food before giving it to her. Same with things offered onto her tray. We cannot tell her "don't touch, too hot!" she does not understand and will not comply.

When Isla has finished her meal, we need to clean her up and immediately remove the paper towel or washcloth used as she will grab it and chew it. If she gets access to a napkin, paper towel, tissue or cleaning cloth, she will grab it quickly and sneakily stuff it entirely into her mouth and choke on it. There have been times we weren't watching closely and were unaware she had stuffed something into her mouth until she started giggling and choking.

After breakfast we put her in her stander equipment. This is vital for her hips and legs to remain strong and grow properly since she can't bear weight on her own without stability support. She must be watched the entire time as she sometimes manages to free a foot and slip herself partially out of the straps holding her body in place. When Isla has finished her meal, we need to clean her up and immediately remove the paper towel or washcloth used as she will grab it and chew it. If she gets access to a napkin, paper towel, tissue or cleaning cloth, she will grab it quickly and sneakily stuff it entirely into her mouth and choke on it. There have been times we weren't watching closely and were unaware she had stuffed something into her mouth until she started giggling and choking. She also stims so hard she can roll herself into furniture and damage it from incessant banging, or access things on furniture that is not safe for her. She stays in her stander for a couple hours in the hopes it will encourage her body to have a bowel movement. If she poops while standing, there is a much greater chance we can avoid the almost inevitable blowout that will occur if she poops while seated or lying down. If she poops while playing freely on the floor, 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. If she blows out, this requires carrying her precariously up our stairs and plopping her in the bathtub, scrubbing her, the tub and her clothing (as well as any equipment or area that also got soiled) all the while trying desperately to keep her hands, mouth, hair and ourselves from contact with the brown clumps of doom. 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.

At lunch she is placed back into her activity chair and same as the breakfast routine, someone must watch her while another person prepares her food in the kitchen. She must have constant

monitoring while she eats to ensure she doesn't choke. She requires someone to spoon feed whatever food she has been given and remind her to use her hands to feed herself finger foods. She must then be cleaned up and entertained in her chair or put on the floor for free time where she can get into All. The. Things.

Despite her significant hypotonia, Isla is a determined little girl who works hard to find ways to roll and scooch herself around her surroundings and gain access to tasty afternoon snacks--- things like flip flops or tennis shoes, entryway rugs, computer cords and power strips, dangerous toys the other kids were playing with... even the baby in his equipment. Were it not for super speed parental ninja interventions, 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 as she pulls and tips equipment over and puts herself in places where she will get bonked. She also enjoys gnawing on the corners of our coffee table or the cushions of our couches. She recently gnawed on the corner of the coffee table and somehow (possibly because she was stimming, or possibly because she bit too hard and jerked back in response) managed to pull her bottom two teeth almost entirely out. We had to rush her to the dentist who pulled them the rest of the way out as there was no way to save them. Fortunately, they were baby teeth, but there is concern it may have caused trauma to her permanent teeth and was a terrible experience for all involved. We have yet to confirm the state of her unexposed permanent teeth since Isla cannot follow instructions and would not cooperate to let the dentist take any successful x rays. This accident happened while she was in my presence... but I was distracted nursing the baby.

Isla is also very fond of books, but due to her gross motor impairments and inappropriate chewing habits, she is guaranteed to end up destroying and likely consuming any book she can access, and now that she is much taller, she is able to reach up and access books on our shelf if we are not vigilant. Her brother made the mistake of leaving his math book on the sofa one time and she literally ate his homework. Apparently, Pre-Algebra has a really good mouth feel.

Isla also adores any screens... tv... phone... computers... and will aggressively seek access to our phones and laptop. She tends to bite our phones and has successfully pulled the laptop off the table and down onto herself and the floor at least once and unsuccessfully attempted many other times. She will go after cords and attempt to chew those or get herself tangled up in them. She has no safety awareness and could easily unplug things and get into trouble with the power strips. We also have to watch her with her own hair as 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.

Dinner routine is the same as breakfast and lunch. She requires constant supervision and full assistance. When it is time for bed, she must be carried back up the stairs, bathed if she is dirty, diapered and dressed in her pajamas. Isla does nothing to assist in a bathing ritual. She must be hoisted into and out of the tub, she will not follow any instructions, and often fights and splashes vigorously while giggling because she likes the stimulus of the water and freedom of movement. She would easily drown herself, if we were not there to supervise. This is something my husband must do as she is now too big and too heavy for me to manage lifting and manipulating her into and out of the tub (especially during my last pregnancy and recovery). Once bathed and dressed, Isla must be lifted into her bed where we attempt to position her well and cover her, but she often sits up and moves around, and occasionally wedges her limbs or her body in a position that she can't get herself out of. We have to move curtains, cords, baskets, etc. out of reach from her bed as she has grabbed and attempted to eat or entangled herself in all of those items. We also have to cover her bed rail with a blanket to prevent her from doing damage to her teeth and the bed as she frequently gnaws on that. Once put to bed, she will often cry and require multiple visits being carried up and down the stairs if she refuses to fall asleep... often due to what we assume is digestive distresses. She will wail and squirm until she finally falls asleep again and we carry her back up the stairs and lay her back to bed.

Because of her cognitive impairments and severe disabilities, it is extremely difficult to take her anywhere or go enjoy normal activities as a family. Even things as simple as playing on a playground require lifting Isla into and out of her stroller... hoping the stroller can traverse playground terrain and then carrying her around the playground with full support in order to enjoy use of the playground equipment. If we want to go to a social event, one parent often has to stay with Isla outside of a concert or wedding or event that requires times of quiet. Her vigorous stimming and vocalizations are loud, disruptive and cannot be quieted. When we attend our church, it is extremely difficult to leave her in a classroom or in the care of others because of her size, her behaviors and her overwhelming physical needs. -

We recently had an unexpected emergency hospital visit during the birth of our baby and my husband could only come for brief visits to see us in the hospital and NICU because we only felt comfortable leaving Isla in the care of her professionally trained teachers for the few hours she was at school. We never go on dates because it is too hard to find a sitter who can handle all her needs and the few family members who live close by find it very difficult to manipulate her heavy body due to age or their own physical disabilities.

We love our daughter dearly and probably the most difficult reality of her condition is lack of communication, low muscle tone and difficulty with digestive issues. SO many of her disabilities are a result of her low muscle tone. We would love to find a way to better understand how to help her have less digestive distress and less stressful eliminations and clean up. And when she does have a gas attack, we would love a better solution to help her through it than our current habits of using essential oils, belly rubs and just holding her and comforting her as best we can.

Thank you for your time and for hearing our story.

Karen B., parent of a 22-year-old daughter living with PMS

Comment 1:

1. Most significant symptoms of Phelan-McDermid Syndrome: Regression/Catatonia/Bi-Polar/Neuropsychiatric illness, anxiety, rage, loss of social skills, and loss of communication.

2. Best Day- Kimmy is part of our family, participating in activities like camping and riding quads, enjoying life with a big smile on her face!

Worst Day-She is full of anger and rage, withdrawing from life, choosing to stay in bed and not join with her family or friends.

3. 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.

Family outings have all but become non-existent, including going to church, eating out at restaurants, and other family social activities and vacations.

4. Kimmy's ability to cope with her symptoms over time has done a complete 180-degree turn. Through age 19, she was able to take on the challenges of being a special needs kiddo like a trooper. She tried new things, loved meeting new friends and doing her best to participate in all things life threw at her, with a big smile on her face. She was even able to work at a job with minimal supervision! After she turned 20, it was like a switch turned off for her in her head. She became very anxious of many things, including those things that she had been very comfortable with just days and weeks before. She lost all the gains for independence she had made over the previous 19 years of her life. She withdrew into a shell of herself, and we lost her smile and hugs. Our 22 year old daughter that we had encouraged for years and helped train for semi-independence, is now lost, back into the early grade school years, needing help with everything, bathing, dressing, eating, getting into a car and safely buckling her seatbelt, the list goes on. She is no longer able to cope at all!

5. We are at the beginning of two plus years of our new normal. Doctors have difficulty diagnosing what's going on with this patient they do not know. They see her as she is now, unable to understand what all she has truly lost, because they did not know her when she was the happy, engaged and involved high school student years ago. We try the protocols they have given us, and see no signs of Kimmy's heart and enthusiasm for life. We try the next treatment up for discussion, and to no avail, Kimmy has not come back. We have to watch our girl that was so full of life just continue to fade away. Every once in awhile, I catch her eyes, and I say, I see you in there. We are fighting to get you back! She walks like an old woman, with no plans or dreams to look forward to...Hospitalizations, antidepressants, anti-anxiety meds, we are juggling to help her survive. 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 2 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!

Comment 2: Medication treatment score would have been not at all, until our doctor finally reached out to the ECHO team a couple of weeks ago. Some relief and hope again!

Denise K., parent of a 40-year-old son living with PMS

Comment 1: Best days-smiling/laughing, can stay focused long enough to complete an activity such as getting dressed, calm enough to go out in public, sleeps at night.

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.

Comment 2: Symptoms with most impact: fragmented sleep =sleep deprivation, seizures and injuries from falls from seizures. Voice volume (yelling, laughing, other loud vocalizations) = limited places one is comfortable living, nonverbal=frustration for my son and leaves everyone guessing.

Comment 3: 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.

Comment 4: We have not found a pharmaceutical treatment that has been effective in addressing fragmented sleep, mood swings, dysregulation, or OCD. Some have made his condition worse. Dre has gone through many seizure meds, some have caused complications, such as Stevens-Johnson Syndrome, hyperammonemia, severe hand tremor and low platelet count. Seizures are never fully controlled. We have never been able to get a good EEG (longer than 20 minutes) as Dre will not tolerate the leads on his head. Dre will not tolerate anything on his skin, such as a band aide, a cast on a broken foot, an IV, etc., so any type of treatment requiring such things are challenging to impossible for both Dre and those who try to treat or care for him.

Comment 5: Yes, concern about the future and finding caregivers that will provide your child with a good quality of life. Very challenging when your adult child does not sleep, mood swings which can manifest with aggression and property destruction, nonverbal, won't wear clothes in the house, manage appointments, medications, etc.

Comment 6: Treatments/accommodations/supports: 2-D pictures, iPad and iPhone with communication app, schedule app, other visual supports. Use of a head protector beanie or headband (the type ice skaters use) to protect from falls from seizures (Dre won't wear a

helmet). Dre takes supplements to support his liver, tried CBD for several years for seizures and sleep, not effective for either, a regimen for bowel regularity: stool softeners, Citrucel, prune juice, ample raw fruits and vegetables, probiotics and fiber gummies. Padding on corners and furniture edges, most of which he has ripped off when in an "angry" phase. Non-breakable glasses and dishes, cutting food up small as will stuff his mouth and not chew well (doesn't move food around with his tongue, just chomps a few times). Replaced a window with non-breakable glass after punching it out. Melatonin for sleep-does not keep him asleep. Camera that records in room he sleeps in to monitor seizures and sleep. Baby monitors for staff to keep an eye on him when he gets up at night. Many seizure medications over the years, currently on 4, and a VNS implant-some reduction in fx and intensity but still occur; they change over time. Staff training on Dre's needs, supports (communication, hygiene, sensory needs, behavior interventions/de-escalation strategies, sign language, etc.).

Thomas S., parent/caregiver of an individual living with PMS

Most significant are lack of communication possibilities due to the lack of mental development, Fear of febrile convulsions and uninterrupted attention due to the lack of awareness of danger.

Callio, parent of a six-year-old daughter living with PMS

Hello!

My six year old daughter has Phelan -McDermid syndrome.

1. The symptoms with the most significant impact on our life are:

- difficulty in learning and achieving new skills

- lack of speech/ non-verbal

2. It is difficult for a parent during every day to be optimist about the future and to stop worrying about his kid's life. Our best days are when she is happy, friendly with acceptance in learning.

Our bad days are when also we are pessimist and tired about trying to help her and improve her skills and social life.

3. Leading - writing - Speech - life skills - jumping

4. As she keeps learning slowly but stably, she becomes more capable to "communicate" her feelings and do some things by herself.

5. Speech therapy - ergotherapy - swimming

6. The treatments help her, but they cannot help in the radial way her life, improving the learning skills.

Anita, mother of a 10-year-old daughter living with PMS

I have a 10year old daughter with PMS. Specific activities she had difficulties with are learning toilet activities, getting dressed by herself, fear or swimming and the sea.

Her main issues concern speaking and writing. She has been doing well in school, and had big progress with the help of communicator and clevy keyboard

Shelley T., mother of a 20-year-old son living with PMS

The symptoms with the most significant impact on my son with PMS are: 1) Sleep Disorder. Sam has not slept through the night since birth. He is 20 years old. The impacts that lack of sleep has had on him and us caring for him are devastating. 2) Lack of Communication. Not only is Sam non-verbal, he lacks any form of communication. We have tried so hard through the years to improve his communication, but he doesn't grasp any method (PECS, Sign or Communication Device). The lack of being able to communicate has led to suffering for him because we can't determine what is going on. Treatments for illnesses have been delayed as we try to determine what exactly is wrong. 3) PICA My son's pica is considered life threatening. He will put everything in his mouth and as a result has had multiple surgeries to remove foreign objects. 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. His PICA is extremely dangerous and requires near constant supervision to keep him safe.

Our lives are completely different than they would have been if our son didn't have PMS. Sam's interests in the world is very limited. As a result, he refuses many activities that we as a family could do outside our home. 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.

Sam doesn't have an understanding of his disorder. He doesn't understand when he needs to do something that he doesn't want to do. As he has grown, it is harder and harder to get him to participate in activities that are not his preferred.

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.

Unfortunately, no treatment has been able to address Sam's most significant symptoms of PMS. We have tried so many medications with minimal improvements. No sleep med we have tried has helped. Nothing seems to help his PICA or lack of communications. We need treatments to address these aspects of PMS.

David and Maryjane, parents of a 31-year-old daughter living with PMS

At the age of 26, our daughter (now 31) began having periods of agitation that at times have progressed to aggression. She continues to live with us at home, and this has had a tremendous

impact on our lives. We never know what kind of day it will be. At times, we are able to go out as a family to restaurants, grocery shop, attend family events, etc. Other days we are housebound, struggling to get through the day. She no longer can attend her day program on a consistent basis. We feel her behavior at times is directly related to her bowel regime, so it is a constant struggle to see that she has regular bowel movements that we manage with Miralax. She currently takes Seroquel and Prozac which have provided minimal relief.

Our hope and prayer would be some kind of intervention to help our daughter live a happier and more fulfilling life. Thank you for your interest in PMS.

Karen D., grandmother of a five-year-old granddaughter with PMS

Comment 1: Everleigh my granddaughter is five- she is nonverbal which makes it hard to tell when she is in pain you don't know where she is hurting or what meds to give. Second, she has fecophilia so she has to wear onesies and have a caregiver so she doesn't get her hands there to eat and smear feces everywhere. She also is a safety risk- she climbs on things, falls off hurting herself and knows how to open the front door and run into the street. My daughter is a single mom and has to work so she has EcH in the day and respite in the evenings. When the state hours run out it is very expensive. She has two older non-PMS siblings which love her and care for her but many times they cant go to activities as a normal family due to Everleigh. It is difficult to travel with her. She is very happy most days and loves to play outside but she needs 24/7 caregiver. When the caregivers can't come I try to help out but if I cant it is very stressful for my daughter to try to work which thankfully she works at home. I want to mention that my son in law could not handle this and this resulted in the divorce.

Comment 2: No one has mentioned leucovorin oral for autism my granddaughter takes that everyday it helps with her attention and behavior.

Josh, father of a son living with PMS

The symptoms of PMS that have the most significant impact on my sons life are: 1) Nonverbal 2) not being toilet trained and 3) PICA-he puts everything in his mouth.

Amanda, mother of a son living with PMS

Nonverbal, toileting, pica, toe walking and gastroparesis are symptoms currently making the most impact.

Brigitte, mother of a son living with PMS

- GI issues, being unaware of safety and hypotonia affect our child the most. Being non-verbal is also a challenge unless surrounded by people who understand her non-verbal communication and AAC.

-Our best day she has no reflux and is generally content. She can spend time on her own, sleeps well etc. If she has reflux or migraines she is clingy, cranky, in pain and does not sleep well. This affects the whole household.

-All activities take a lot of planning.

-once treatment for medical conditions and alternative communication has been implemented, she is coping better.

-we try not to focus on PMS but rather consider what children her age would be interested in or doing. We don't treat her like a baby. We observe her and focus on her interests while keeping "typical or age appropriate" interests and milestones in mind.

-speaking with her mindfully, like a fully aware person has boosted her confidence and she is becoming more social. She is in kindergarten and doing regular things, being included wherever possible. We continue to treat medical conditions as needed but choose not to focus in the medical aspects unless relevant or necessary. We never allow "what if" conversations to take stage, as they are not reality and can bring fear and anxiety in our home. We choose not to be victims to PMS.

Mark, parent of a daughter living with PMS

Comment 1: Most Problematic Symptoms:

1) Intellectual Disability

2) Autism Spectrum Disorder

3) Hypotonia

Comment 2: An issue I am hoping will be resolved with upcoming clinical trials is the ability to continue using the treatment if there are noticeable improvements. I have a hard time imagining my daughter's condition and mental state being improved only to take that away while the trial is being completed.

Michael, parent of a child living with PMS

As a parent of a child with Phelan-McDermid syndrome, the symptoms that most impact our lives are 1) intellectual disability, which impacts the ability to independently overcome 2) Gut issues, and 3) Sleep issues

Penny, mother of a six-year-old daughter living with PMS (5.99 kb deletion)

Comment 1: Artemis, 6 years old, deletion size 5.99

Most significant problems for now are hypotonia (walks but limited saving reflexes), no danger awareness and being non-verbal. The biggest challenge is how to make quality of life better for both her and us. She had her first febrile seizure a month ago. She uses a communication device

and goes to an inclusive mainstream school. Big impact on her motor skills has been seen with MAES therapy. We are pushing her to become literate.

Comment 2: How does Phelan-McDermid syndrome affect you or your loved one on best and on worst days? Describe your best days and your worst days.

Best day: she has slept well, has had a bowel movement, doesn't have reflux, has actively participated in school lessons.

Worst day: awake for many hours at night, constipated. These things stop her from being able to chew her food, swallow her water, focus on any activity, pacing all day, loses her balance or throws herself on walls and the ground without caring about safety.

Comment 3: Are there specific activities that are important that you or your loved one cannot do at all or as fully as you would like because of Phelan-McDermid syndrome?

Walk without having someone shadowing her in case she falls. Listen to her speak some words, being able to point to show us what she wants

Comment 4: 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

Comment 5: I am very worried nobody will protect her when I am gone, give her the care and stimulation she deserves. Also, sexual/physical abuse soars in the disabled community in care homes etc and she won't be able to tell anyone or advocate for herself.

Comment 6: MAES physical therapy and being in a mainstream school have helped

Comment 7: Science is clear that GI health and brain functioning are interconnected, so improving gut health would positively impact cognition and communication. Big impact on her motor skills has been seen with MAES therapy. We are pushing her to become literate.

Joan, grandmother of a boy living with PMS

My grandson’s delays are a major cause of concern for his quality of life and the stress that it puts on his loved ones. I want to learn as much as I can about PMS in order to continue to see improvements in his progress and quality of life.

Laraleigh, mother of an adult son living with PMS

Comment 1: *Of all the symptoms of Phelan-McDermid syndrome, which 1-3 symptoms have the most significant impact on you or your loved one’s life?*

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. He's making progress but this has changed our lives.

Comment 2: *What are you currently doing to manage your loved one's PMS symptoms?*

My son is presently institutionalized after a manic episode that lasted months. He has been institutionalized for over 1 year. He is on a cocktail of psych meds and gets monthly IVIG treatments. We are ready to get him home, but there are no services in our state to make that safe or possible. I visit him every 2 weeks.

Comment 3: *How does Phelan-McDermid syndrome affect you or your loved one on best and on worst days? Describe your best days and your worst days.*

When things are great, Lu is funny, happy and cognitively aware.

On his worst days, he is manic, refuses to sleep, chokes on his food, has toileting accidents, and is aggressive to others.

Comment 4: 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

Comment 5: My son's experience with PMS has had an immense impact on him and the lives of our entire family. My son's neuropsychiatric symptoms robbed him of all of his skills, ability to communicate and he presents with severe mental health symptoms. He and many like him deserve support and therapies and treatments.

Breallyn, mother of a daughter living with PMS

PMS affects every moment of Imogen’s life, and every moment she interacts with the rest of the family.

One of the most significant impacts is on her executive functioning and ability to understand and engage with everyday life. Imogen basically needs someone to interpret the environment for Imogen and give her a constant stream of guidance and encouragement to undertake the tasks of the day.

This can be anything from “let’s look at your visual schedule to see what to do to get ready for school” (followed by one-to-one focused help to complete all the steps such as dressing, eating breakfast etc) to “you are feeling upset because there is two minutes to wait until your Carer arrives. Let me help you wait” (followed by a desperate attempt to distract and redirect her from having a complete meltdown with self-harm and harming the people trying to help her)

Caring for Imogen is very intense, focused work. You need to exclusively focus on helping Imogen live her life moment by moment, and you cannot get distracted by your own needs or those of anyone else. This has had a cumulative and detrimental effect on our family as we struggle to meet the basic needs of our other three children, and we grasp in vain for any normal, balanced way of life.

Carrie, mother a son with PMS

Comment 1: My son has had an incredibly hard journey with Phelan-McDermid. Last year Gavin started having seizures, unfortunately the doctors didn't treat these aggressively and sent us home and were told to "train him not to do them". Obviously, you cannot train someone to not have seizures and his condition worsened over the month we were home. He started to lose the ability to feed himself, walk and several other new issues. The doctors finally let us come back to the hospital and there we stayed for 96 days, 38 of which were spent in the ICU. We regained some control over the seizures, however he has spent an additional 100 days in the hospital since as feeding issues and the seizures have returned. 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. He does not sleep at all, which has impacted us beyond measure as someone has to be awake with him at all times. I cannot impress upon you how incredibly difficult it is to manage his care, work and take care of his needs. My state doesn't have a lot of resources to assist us. Michigan is a terrible state to live in if you have a child that has severe and complex medical needs. I have had to fight for what little nursing I can get to assist us. I am exhausted to the point that I can no longer function effectively in everyday life. I have had two minor car accidents due to lack of sleep.

Unfortunately lack of resources is not the only issues we have dealt with. Our insurance company continues to deny his medications, EEGs, hospital stays and several other things that they should be held accountable for, but chose not to. The insurance companies are constantly revoking his prescriptions causing us to have to file appeal after appeal. We are already dealing with a terrible situation made worse by the greed of companies more concerned with shareholders than policy holders.

Comment 2: This is my second comment as I would like to add more to this discussion.

My Gavin is now bed-ridden he cannot sit up, roll over or walk. He no longer has purposeful movement and we have been released from Physical Therapy, ABA therapy and school programs due to lack of progression and his current medical status. Our team thinks that he is overall declining and has mentioned hospice as an option due the refractory epilepsy. We have fashioned his therapy room into a first floor bedroom where either my husband or I sleep every night to monitor his medical needs. Someone has to be in this room at all times. His seizure regimen consists of meds given at 9:00 am, 3:00 pm, 9:00 pm, 10:00 pm and 3:00 am.

Blaire, parent of a seven-year-old daughter with PMS (small *SHANK3* deletion)

Our seven-year-old daughter has Phelan-McDermid syndrome. The most difficult symptoms are her inability to communicate and her tendency to put everything in her mouth at all times and her lack of safety awareness. After having over a dozen words and phrases for many years she is now nearly completely non-verbal - that regression has been incredibly difficult.

After years of progress she has lost many skills including coloring, cutting, and speech. She is also not potty-trained. Even though she has a small deletion of partial *SHANK3* she has been significantly impacted.

On our best days our daughter laughs and smiles and enjoys being outside and going for walks with our family. She loves climbing and enjoys playgrounds.

It is difficult to go out to eat with her or go to social gatherings because she may run away or take others food or eat non-edible items and she must be watched 100% of the time.

Right now, we work to manage behaviors like eloping and eating non-edible items and have OT and speech services. However, primarily we need to always be with her in very close proximity to ensure her safety.

We worry very much about her future and hope for treatments to enable her to gain independence and communication skills and live in her community.

Janet, mother of a daughter with PMS

Comment 1: Psychiatric, gastrointestinal, and neurological issues are our biggest hurdles.

On our worst days we are dealing with chronic constipation or massive diarrhea, and bipolar behaviors that keep us from working or even leaving the house. As a parent I have caregiver PTSD as I'm constantly on edge that she might suffer a psychiatric crisis at any time.

As my daughter has aged I see that her immune system is breaking down, she's getting way more viral infections. She has Neurogenic Orthostatic Hypotension, so any viral infection causes her blood pressure to drop dangerously low.

She is on so many medications to manage psychiatric issues. She was diagnosed with osteoporosis at age 24. She is taking an annual infusion along with two prescribed medications and two supplements just to manage that because we need to protect her kidneys still.

We have to constantly weigh any treatment or medication against how it will affect another system.

Comment 2: 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.

Kevin, father of a 23-year-old son with PMS

I would say the biggest challenge we now face with our 23-year-old son with PMS is losing skills learned when he was younger. His speech has gone from maybe 100 words to less than 20. He has also become incontinent, which makes outings very difficult as he is 6' 2" and 180 lbs.

Julia, mother of a five-year-old son living with PMS

1. autism, no language, sleep disorder

2. Best day: He says: Mama an can walk

Bad day: Fall from the stairs, Hospital

3. We Can't take time whit family by dinner, because He wont sit and run all the day, our marriage broke up after 10 years, because we had no time to sleep or for us, he needs always help, its a hard job

4. We are much more patient and can respond better to his emotions

5. For bester feeling we get's CBD oil and Biotin

6. It's not the medicine he needs. We are not allowed to give insulin for health reasons

Comment 2: activities: my son is 5 years, he don't like tv, you tube or music

he only loves door, to close an open, is really high euphoric and bad angry if he can't open the door, stereotypic behavior, all the times on all places

Greg, father of a 9-year-old daughter living with PMS

Comment 1: Most impactful symptoms: 1 Potty training still in diapers at 9 y/o, 2 Communication

Comment 2: Treatment issues: We have been using ABA for a few years. We are uncertain of how effective it is. 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.

Teresa, caregiver of an individual living with PMS

Comment 1: Please correlate age of diagnosis with type of chromosomal disorder and current age, to see whether this hypothesis is true: Older patients with *SHANK3* variants were diagnosed later, and PMS may be being missed in older patients.

Comment 2: IVIG has been tremendously helpful for several of our patients, including my own. It is hard to get it covered.

Comment 3: Preventing regression; it is the great terror.

Tanya, mother of a daughter living with PMS

Toileting!! 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. If this does not work, I spend the entire time worrying about when she will have a bowel movement. My cortisol levels are off the chart because of always worrying. Also, swimming diapers. There are many for children under 40lbs and some for adults over 80 pounds but very little for that in between 41-79punds. As her caregiver toileting and potty training are my everyday WORRY. We do things anyway but as her caregivers my husband and I rarely have fun.

Anna, mother of a daughter living with PMS

Comment 1: We struggle with extensive developmental regressions (going from a full range of fine motor skills, interpersonal skills, and spoken language to very basic and low cognitive functioning). It is difficult to both understand the regressions and anticipate what growth or learning we might be able to anticipate.

Comment 2: 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.

Comment 3: 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 1 to provide her with a safe stable environment, while her siblings are active in the community, travel, etc.

Shawna, mother of a daughter living with PMS

Comment 1: Most challenging symptoms for our daughter and family:

- epilepsy with drop seizures

- cycles of constipation

- sleep disturbances including night awakenings

Comment 2: Another concern is the health of the parents. Many times this is neglected and parents don’t have the time and energy to take care of their own health and exercise needs. Even though we want to be as healthy as possible so we can look after our kids for as long as possible.

Comment 3: One challenge of attending therapies is that my daughter can be uncooperative or experience discomfort due to constipation during the session, rendering it ineffective. Speech therapy has been the most difficult to engage my daughter.

Rui, parent of a 10-year-old daughter living with PMS

Comment 1:

1. Non-verbal communication, highly tolerance to pain, intellectual development.

2. The most stress situations are when Elisa "blocks", insisting for something that is not the appropriate behaviour for that specific information, or when nights are a fight to sleep and awakes 3/6 times, asking for the parents or sister. The best days is when she gives us warming hugs and radiant smile, when she is happy.

3. We can't have a normal education path for Elisa and teach her what she would need to have an autonomous life. As parents, we are never at rest as we cannot leave her by herself as we could for a neurotype child.

4. Your daughter has 10 years and over time, she has matured being more calm and having more attention, what has permitted to do therapies with her. We can also do some calm social life, but it is still not possible to do things that might last more than a couple of hours as her focus will be lost.

5. The managing of the impact of PMS within our family is a daily challenge, with exhaustion of Parents and also sibling stress as our daughter is very demanding, always asking for the other family members and as she is non-verbal the way she tries to make acknowledge is physical and it hurts.

What we do to help us is to drain all our economies to therapies to cope with her difficulties.

6-. The therapies help with behaviour issues, but do very little relating communication and development issues

Comment 2: My hope for future treatment is that synapses are recoverable and my daughter will improve intellectual development and be able to express vocally her thoughts and needs.

Carlos, father of a son living with PMS

Our biggest fears are how to keep Matthew's seizures under control and keeping up with his GI issues.

Dottie, mother of a five-year-old son living with PMS

Comment 1: For a worst day scenario, his inability to communicate, his high threshold for pain and his temperature control issues along with requiring a g tube and pump for meals all factor into a night where he wakes crying, burning up (107+ temp), and projectile vomiting his dinner. Where do you start? what is happening? is there an infection? Is this just a virus? Does he have too many blankets? Is the A/C out? Did he reflux and aspirate triggering coughing and then vomiting? Or, is something else happening?

The unknown is really scary and stressful. Worse though is that you probably will never know.

On our best days, he is happy and giggly and cuddly. He depends of us for every single moment of his sweet life. He is our 5-year-old newborn, requiring diaper changes, feedings, burping, bathing, and sleeping. But unlike a typical newborn, he needs help learning to swallow, chew, control his head movements, sit, move his limbs, bear weight through his arms and legs, and stretching his muscles. He is a full-time job, even on his very best days.

Comment 2: With my older children, "this is just a phase" has gotten me through the long, hard days. 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. 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.

Jen, mother of a 20-year-old son living with PMS

Comment 1: The symptoms that have the most significant impact on my PMSer's life are GI issues (severe constipation sometimes requiring hospitalization), neuropsychiatric issues (mania, depression, weight loss, no sleep) and lack of communication coupled with high pain threshold making it extremely hard to know when/if/what is bothering him when he is distressed.

Comment 2: Our 20-year-old son was diagnosed with R22 at 14 months old (no mention of PMS at that time) in 2003. We were told he was 1 of 80 people worldwide at that time and that not much was known. We were told to try everything and anything in terms of improving his quality of life. We started OT, PT, Speech, Early Childhood Educ., Feeding Therapy, Hippo Therapy, Water therapy, and Augmentative Comm therapies. It wasn't until 2010 that we learned that he had a diagnosis of PMS. He was diagnosed with hypotonia, reflux, cortical visual impairment, a horse-shoe kidney, and a large arachnoid cyst near the cerebellum. He is non-verbal, has an autism diagnosis, has severe food allergies and moderate seasonal allergies, and has trouble sleeping. A glioma and schwannoma were found during a routine MRI to monitor the arachnoid cyst. We do not currently have a diagnosis of NF2. This past summer he suffered from his first neuropsychiatric episode. He went three days sleeping a total of only 5-6 hours, cried for the first time since he was a baby, was manic (almost seemed uncomfortable in his own skin), couldn't settle, stopped eating, and lost 35 lbs. We started Trazadone to help with sleep and are currently using Abilify to help manage his behaviors during the day. He currently shakes like he has Parkinsons' but we do get glimmers of our boy every now and again.

This diagnosis not only affects our son. It has made a huge impact on our family - what we are able to do and how we live our daily lives. An improvement in ANY area would be an

improvement in all of our lives. These children deal with so many challenges each and every day and deserve so much better. We are so appreciative of your time, your consideration, and any help that you can provide for our very deserving and inspirational children.

Emily, mother of a daughter living with PMS

Comment 1: My daughter Frances is very mobile and somewhat verbal. 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 I'm parking lots about elopement and am on high alert every time we leave the house.

Comment 2: Therapies (speech and physical) have helped Frances function day to day. We are able to communicate with her and she enjoys typical kid things like playgrounds and trick-or-treating. However, none of her therapies have made a huge dent cognitively. She is years behind her peers in terms of education and knowledge of the world and how she fits in.

Cat, mother of a son living with PMS

We also almost lost our son Cree to seizures on September 1, 2021. He coded blue and had to be bagged. He made it through because he was in the ER when it happened. We worry every damn day about SUDEP. He has lots of seizures as well as a laundry list of other issues, many of which have been mentioned in your polls. PMS is terrible, and we desperately need more funding for research.

Cathy, grandmother of a granddaughter living with PMS

The diagnosis of epilepsy was a game changer, as Madison's seizures often required trips to the hospital to control them. Her current medication has kept her seizure free for about 8 months. As her grandmother, my husband and I are the only people that my daughter and son-in-law trust to babysit her and her twin sister. This has had an impact on my daughter and son-in-law's ability to go out without the kids or for them to trust taking Madison anywhere too far away from a hospital that they trust.

Amy, mother of a 17-year-old son living with PMS

Comment 1: Top troublesome PMS related health concern currently is seizures, which started for us right before Logan's 17th birthday. Ethan Walls life story just drove that point home for me. He's had two [seizures] in 4 months and they were big ones, gran mal. The last one he had we had to administer rescue meds as he was turning blue. Communication is the second most troublesome as 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.

Comment 2: 6 months ago seizures would not have been in my top 3. Since starting seizures 4 months ago (at the age of 16) it is front and center in my mind. This question makes me realize

that PMS is an evolving disease that seems to constantly shift whether it be in symptoms or regressions.

Elizabeth, mother of a 24-year-old daughter living with PMS (full *SHANK3* deletion)

My daughter, Becca, is 24 with the full deletion. My biggest worry is how the hypotonia as affects all her systems from GI, lymphatic, metabolism, circulation, as well as the neuromuscular. Her inability to communicate what is "wrong" about these issues makes daily life the most difficult. Often the issue becomes more critical before we can determine the problem.

Ro, parent of a 13-year-old daughter living with PMS

Living with PMS and symptoms and daily impact Answers

1. Autism and processing disorder are severe. Lack of speech and communication. Bowel issues are quite severe and she is often in pain because she can't poop and we have to be very strict with her food intake and intolerances. Sleep issues can be very difficult for our family. Hypotonia is a huge issue for her and hinders her from taking part in a lot of outdoor activities and we have to support her continually. Issues with feeding too, we always sit with her when she eats and have to cut everything up otherwise she may choke. Issues with thermoregulation too, both very sensitive to cold and heat. Lack of awareness of danger. Lymphedema. I have so many more, I cannot put down to three I am sorry.

2. On her worst days she screams and cries constantly and we may have no idea what is wrong. Sleepless nights for sure. No cooperation and no way to calm her for more than a few minutes. These episodes can last up to months. During those episodes we run every possible test and visit all doctors until we find what is wrong, if we do at all.

On a good day, she is happy and calm and needs our full attention and support. Our moto is “at least she is happy”. That is the only thing that keeps us going. Keeping her safe and happy.

3. We are definitely more equipped with knowledge as she ages. But as she ages, we age too, and it is becoming difficult on our bodies to cope with a teenager that essentially is at the age of a toddler mentally.

4. 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. She gets easily tired when outside so she cannot take part in walks in nature that she loves, she cannot be exposed to hot weather and we live in Greece.

5. The constant worry for us is her well being and what is going to happen to her when we are not around any more to take care of her.

Regression is a major worry for us too. We are constantly expecting for something to happen in terms of health that will cause her to regress and it is constantly happening, it's a tango, two

steps forward 1 back, 1 forth, two back and so on... She is completely inconsistent in everything.

Susan, mother of a 35-year-old daughter living with PMS

Comment 1: My daughter is 35 and has significant intellectual disability. But her psychiatric diagnosis-bipolar disorder-is what really prevents her from living her best life. In middle school, when she had her first episode of mania, she was out of school for months at a time. She lost all her friends, and was unable to participate in the sports and other activities she loves. She was up all night for weeks, and I spent the nights sleeping at the top of the stairway so she couldn't go downstairs and get hurt. Over the last years she's had 3 major psychiatric episodes, each lasting many months. Currently on multiple psychotropic drugs. She is doing well, but we live in fear that her life will fall apart again.

Comment 2: "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. At one point we had to take her off two of the meds (long story), and over the next months she again became manic. We restarted the drugs over many months, and she improved again. Despite the heavy medication load, she has been able to run two half marathons (slowly)!

Stephanie, mother of a five-year-old son living with PMS

Our 5-year-old son was diagnosed with autism at age 2 and PMS just 10 months ago at age 4.5. He is a delightful boy who loves ABA and looks forward to going to school every day. He loves the climbing gym, slides and reading with grandma and grandpa on FaceTime. 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.

We are so hopeful that new treatments will become available if the strides we have made disappear or if new complications related to PMS develop. We are participating in a drug trial currently and have felt so grateful to be able to access a possible treatment as well as to get to know a community of researchers who are working so hard to find new treatments for our kids.

Martha, mother of a nine-year-old son living with PMS (two *SHANK3* variants)

Comment 1: My son's name is Matthew Luis. He is 9 years old. He is a fraternal twin. Our other son is neurotypical. Raising twins, it was very apparent seeing all the differences between Matthew and his brother. His brother was meeting all milestones while Matthew wasn't. We began early intervention at the age of 8 months (speech, occupational and physical therapy) and he was diagnosed with autism at the age of 20 months from a neurologist. We began ABA

therapy for 40 hours a week on top of his current other therapies of speech, OT, and PT. We knew there was more delays besides that diagnosis alone so our neurologist referred us to a geneticist. The neurologist did mention Phelan-McDermid Syndrome but really didn't know much about this. We looked it up online but really had no idea. We finally had genetic testing done and after 6 months (He was 2 years 9 months old) got the results of Phelan-McDermid Syndrome - not 1 but 2 *SHANK3* variants. We were lost. We are blessed to have found PMSF which has been an ongoing resource to our family and a constant support. Matthew has never stopped therapies till this day. He continues 25 hours of ABA at his special needs school. He receives 3 hours of speech, 3 hours of occupational, and 3 hours of physical therapies every week.

Even with all these intense therapies over the years, he is still non-verbal and has global developmental delays. He walked at the age of 3. He has very hypotonic and falls countless times. He has high pain tolerance. He has no safety awareness. He has no coordination or motor planning. Being non-verbal, he has become increasingly frustrated and engages in self-injurious behaviors. He becomes aggressive and tries to hit, grab or bite others. We have tried several communicative AAC devices, PECS (picture exchange communication system), signing, but nothing has worked.

Since a baby, Matthew has had severe colics and acid reflux. He has had several endoscopies and is treated by a gastro-intestinal doctor. He continues to take medication for the reflux. He also suffers from severe constipation which he has been hospitalized for more than once. He needs to take two constipation meds in order for Matthew to not be backed up. GI issues have been one of his biggest symptoms and will be a chronic issue.

The latest symptom from the past two years is being diagnosed with epilepsy. He suffers from "tonic" seizures. The cause of movement and lighting seems to be causing the seizures. We had to recently increase his seizure medication.

Matthew enjoys music, swimming, and playing with his dog. He is a very "social" boy and very affectionate. I wouldn't say he has best days but more like best moments - short and sweet moments in between all his daily challenges.

In order to manage Matthew and all his needs, I have left my career of education in order to be his full-time caregiver. As he gets older, he has more needs and more care. Our quality of our family life is affected DAILY for us as parents and his twin brother. Everything we do has to be planned around his needs and schedule. We are unable to do the things that "normal" families can do like go on a family trip or ride bike, etc. The list can go on and on.

We need treatment for Matthew's quality of life and for all suffering from their terrible rare disease. Please feel free to contact me if you have any questions or for any further discussion.

Thank you for your time and I sincerely hope the FDA will consider this small but very important and growing demographic.

Comment 2: For future treatments, we feel that the priority is improved cognitive functioning, communication, GI issues. This will truly impact the quality of life with the PMS person and their family.

I also want to state that when the time comes for treatment or a hopeful cure that they consider people with PMS that also have another genetic disorder. My son has PMS but has been unable to participate in studies or clinical trials because of his other genetic disorder. There are many people with a PMS Diagnosis that also have secondary diagnosis of something else and they should be considered as well. PMSF was going to work on filtering the Data Hub in order to access that demographic of PMS and other diseases.

Laura, mother of a five-year-old son living with PMS

Comment 1: Our son Harry, 5 is always two steps forwards three steps back, the regression seems constant, he learns something and loses something else. Its always an uphill battle to gain any skills.

Comment 2: OT has been the thing that brought my 5-year-old son Harry on the most, however in the UK services on the NHS are in blocks of 6 weeks and your lucky to get one block funded. Similarly with speech therapy he gets a block each term. We see a burst of improvement when the sessions are ongoing but then when it stops we see the regression. It is difficult to afford these therapies privately, but would love to be able to see if intensive treatment would make a better improvements.

Ellie, mother of a daughter living with PMS

Daily life seems impossible when your PMS child has not had solid sleep in 3 years. After trialing 5 different medications, we feel like there is not way out. All the other issues that accompany PMS seem impossible to deal with, without solid sleep. This leaves our family often split in 2 since we have 3 other children. Outings often seem impossible.

Dinesh, parent of a child living with PMS

Symptoms that affect my loved skills:

1, low muscle tone

2, difficulty in fine and gross motor skills

3, minimum to nil speech and pointing skill

4, severe cognitive skills.

Best and worst days:

Best days:

To be honest, there's no best days, some where due to acid reflux, swallowing issues, digestive issues, chronic pain, disturb sleep…

Worst days:

As I said, everyday is the worst day to be honest…

Specific activity that my loved one cannot do at all because of PMS are;

No speech, none of activity can be do by himself, socialization, communication, mobility, cognition, intelligence, self care, medical and dental care.

How has your loved one's ability to cope with the symptoms changed over time?

To be honest, there's no changes we see in since his birth.

What are you currently doing to manage your loved one's PMS symptoms?

We do all kind of therapies, medication, trying to teach but there's no single improvement till time.

How well do these treatments address the most significant symptoms and health effects of PMS?

Till date, for last four years, we don't any changes or improvement in treatment.

Jay Jay, friend of a parent whose child is living with PMS

Watching a friend whose life is so limited with boundaries and challenging due to her sons PMS. I pray every day that a medical solution will happen and they can live in a way to cope easier with such special needs. Such a life struggle praying the FDA decides to support CURESHANK efforts

Katie, mother of a six-year-old-daughter living with PMS

Comment 1: My daughter Laney is six years old, diagnosed at four. Our lives as a family of four are a completely different life than we could have ever expected. We have realized that high potential that we will be Laney's caretakers for her whole life and that our own lives have changed forever. Laney needs constant supervision and help with daily functioning skills. Because of developmental delay and hypotonia she is unaware of household and outside dangers. We worry about sending her to school and her elopement tendency and choking risk. Laney has escaped our house, barefoot and in a pullup and walked down the street with her three-year-old cousin. Totally unaware of the cars in the street and potential stranger danger. Luckily a kind neighbor spotted them fairly quickly and helped them to safety. It was a terrifying awakening to us. Along with elopement we have had to do Heimlich so many times. Every time is very scary and we worry if we will be able to help her. When we have her in school or with a

respite caregiver we cannot relax, knowing that she could choke out of no where and unexpectedly. Because she takes big bites and does not chew, it does not help her GI issues and constipation. We monitor her diet but even when being breast fed as an infant she suffered from severe constipation. I remember a tiny infant screaming and crying so hard due to constipation that she fell asleep after several hours of screaming due to exhaustion and straining. This was the first time we realized that there must be some type of low muscle tone keeping her from being able to use her GI muscles successfully. She was later diagnosed with central hypotonia that mostly affects her mouth, throat and GI.

We believe this is also part off the reason Laney is non-verbal. When Laney's speech was delayed at 1 year old, we started speech therapy. I remember therapists always trying to reassure us that she would be able to talk "one day". I remember crying, thinking, " how do they know? How can they be so confident?" We knew the possibility of her never talking. She was unable to learn sign language because of her lack of motor planning and cognitive delay. Her receptive language seemed fairly good but her expressive was non-existent. She still uses hand pulling and pointing and jabbering to let us know what she needs. She has recently learned to use her AAC device to communicate basic needs and it has been so helpful. We now are able to understand when she is hungry or thirsty. It has made us so hopeful for her communication skills to progress and it has also made us very aware of how hard it has been for us to help her with her lack of communication skills.

Laney's sleep disturbances has been one of the hardest for our entire family. Myself, my husband (Laney's Dad) and her seven-year-old brother are woken throughout the night from loud screaming, confusion, and very early morning waking. 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. Our most comfortable and easy place to be is home, therefore I feel we do miss out on certain life experiences as a family. Often my husband and I have to divide and conquer in order to provide our son with his social needs while providing Laney with hers. The struggle to be able to provide enough attention to our typical son is real. It is one of our priorities in parenting them but we feel that we are often torn and forced to prioritize our time and attention, which in turn we feel one of our children usually misses out on something that they would otherwise really enjoy or need because of Laney's needs.

We spend our days helping Laney with self care and staying safe. We are lucky that Laney is a happy girl most of the time, despite these struggles. She has very bad days in waves. Usually she'll be doing well for several weeks and then go into a stretch of non sleep and behaviors for several months. We never know when we will be in what phase or how long it will last or IF this phase will end.

Comment 2: Because Laney will be prone to psychiatric illness due to her mutation, we are very scared for her future. Although Laney struggles with so many PMS symptoms, she is a happy girl

for the most part and our biggest fear is that she will experience psychiatric illness during puberty and loose her happy and sweet little self. We are scared to see her experience fear of not being able to understand what is happening to her if she does experience this. It gives me a lump in my throat to even imaging her in this kind of fear and pain. She depends so much on her families love and if she isn't able to get comfort from us I don't know how she will feel comfort. That breaks my heart to imagine.

Comment 3: The therapies that Laney has been doing since early intervention have shown very little help treating her symptoms. The progress we've seen in development have been very little and very slow. We celebrate things as little as her being able to isolate a finger in hopes that it will help her in being able to use her AAC device more efficiently for communication. Daily functioning skills are our focus with her treatments. Self care, communication and safety awareness are our current goals.

Comment 4: Often therapists don't have experience with PMS and don't have the knowledge to understand Laney's needs. We often see such slow progress with therapies that we are always talking with therapists trying to come up with ways we can adjust therapies to get Laney to cooperate better and in turn see better results. I've often found that therapies feel like a waste of time with Laney but because we will never loose hope, we continue to push on and try our best to make the experiences pleasant for Laney.

Sleep training Laney has been such a struggle for the six years of her life. Every attempt to train her has been a full family event with several months of tracking and communication with her doctors. We have seen very little growth in her sleep disturbance but by working for 4 months on eliminating sleep associations we have had several weeks of decent sleep. Only 1 or 2 wakings at night currently. We know that this could be a cycle and are holding on to hope that this training will stick. We are not sure if her Clonodine or our training on removing sleep associations is what is potentially helping. We are willing to try anything but tend to go for the least invasive treatments first.

Meagan, mother of a son living with PMS

Comment 1: Gus has issues regulating his temperature so he overheats easy. We have to always be aware of temperatures/how long we will be out/bringing along cooling vests/etc.

Comment 2: Balancing all the therapies and medical appointments are a challenge. We have on average 2-4 appointments a week. He's had 3 surgeries so far and more ultrasounds than I can count. Lots of specialists. And fighting with insurance refusing to cover needed therapies is incredibly frustrating.

Comment 3: It's hard to celebrate the milestones he achieves because I am terrified of him losing that skill one day. The anticipatory grief of what is to come and what he may lose is with me every day.

Laryssa, mother of a 21-year-old daughter living with PMS

Comment 1: Emily, 21, from the exterior looks like her peers, however, her expressive/ receptive language is delayed. Her cognitive ability is at the level of a 4th grader. She loves animals and her dream job is to be a veterinary assistant. It is a struggle to explain that she does not have the capacity to achieve her dream job. She continues to remind her father and I to get her a math tutor to improve her math ability so she can become a vet assistant. Due to her lack of ability, Emily's dream job will be of a modified fashion.

Comment 2: Emily was diagnosed with ADHD at an early age. We tried several meds and Adderall was the best fit. I was not 100% sure that Emily had ADHD. What I did notice while Emily was on Adderall, she was able to realize the urge to use the bathroom. She suffered from wetting her pants in 3/4/5th grades. Once on the Adderall her accidents lessened. Emily has been on 10 mg from the age 10 to 20 years of age. Our pediatrician wanted to take her off of the Adderall due Emily had being doing well not really knowing if the Adderall was effective. After stopping the Adderall, Emily began having accidents. Our pediatrician was willing to prescribe the Adderall again. The wetting accidents stopped. I feel the Adderall help the synapses connect to signal for Emily to recognize her need to use the bathroom.

At the age of 21, Emily now takes a 5mg dosage. Wetting her pants, did not increase; however, I have noticed her increase of perservation on items. Not sure if an increase of dosage is warranted due to the fact that Emily has been on Adderall for so long and not knowing any affect this might have on her. She remains on the 5mg dose.

Emily constant battle with constipation since a young age. Once she was 11/12 ish, I took her to a gastroenterologist who happened to have a Naturopath on staff. Emily has been on natural supplements to help with regular bowel movements. She takes liquid magnesium and a probiotic. This process has been successful, but my worry is the long-term use of these supplements on her body.

These challenges have taken a toll with the cost of buying these items and making sure we take all these items while on vacation. It would be a blessing not to worry about such meds and supplements to a normal life.

Cynthia, mother of a daughter living with PMS

https://www.youtube.com/watch?v=0DSfVmkiJPw

I wanted to share a video of how neuropsychiatric symptoms affect my daughter. The video shows her baseline and then follows her through an episode that led to catatonia. She has been on Lorazepam for two years following this episode to treat the neuropsychiatric symptoms.

Laura, mother of a daughter living with PMS

My daughter Lily started PT at age 6 months for Hypotonia and at age 1 due to missed milestones, had genetic testing done and was told PMS.

Had early intervention with PT, OT and speech has helped us with what works now as LIFE.

At age 5, she started having absence seizures of staring off spells of 10 to 20 seconds like a statue, tonic jerking in her sleep at night and the scariest Febrile when sick or dehydration can be triggered, overheated, etc..

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.

Having 3 types presented scares us daily and restrictions with activities due to environment factors with not being able to sweat, or regulate her body temperature. In the summer she limits hot places and wears a cooling vest and lots of layers in winter.

Pica is my 3rd of having safe areas because she will chew on anything. She needs eyes on her at all times because of this and not eating /swallowing something that isn't true food. She could get very hurt.

Agnes, mother of a 12-year-old daughter living with PMS

Our 12 year old PMS daughter for the last 6 months is going through slow regression, losing her skills, her speech is declining and she is no more able to use toilet independently (for over 8 years she was able to use toilet independently) .

Her behaviour and anxiety is getting worse as well.

It is heartbreaking to see your child regresses and you can’t help her.

It seems there are quite few cases of regression in teenagers especially with PMS genetic mutations.

Grace, mother of a six-year-old daughter living with PMS

Comment 1: My daughter Lily is 6, diagnosed last year. While she has many symptoms common to PMS. She has many symptoms related to autism, ADHD, social communication, I feel they are somewhat managed by behavioral therapies/speech/OT.

For us, her GI issues/discomfort are the most difficult to manage day to day, and impacts her whole day and outlook, behavior and ability to focus and learn. MiraLAX has really been the only suggested treatment which seems insufficient.

Comment 2: My daughter has many therapies which I think do somewhat help -- ABA, speech and OT and we try very hard to get her to as many hours as clinically recommended. The time constraints are difficult to navigate but also managing her energy levels to ensure she can receive the therapies effectively during the sessions. Hypotonia, background GI discomfort and ADHD meds all impact her daily energy levels and how well she receives the therapies.

Kimberly, mother of a three-year-old daughter living with PMS

My daughter Luna is 3 years old and was diagnosed last year. We struggle daily with her inability to communicate with us, as she is non-verbal. We are working on teaching her to use an AAC device but it's slow going. 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.

Arman, father of a four-year-old son living with PMS

Hi my name is Arman I'm the father of Luis. We are living in a small village in Germany. Luis is 4 years old and was diagnosed with PMS (deletion) at the age of 2 years.

Physically he reached all of his milestones. He had problems with jumping or climbing stairs but this is something what we could improve with therapy.

Luis has no visible conspicuousness. He's non-verbal and has communication issues. Almost the whole day he's walking unproductive through rooms and listen to his toys with music, triggered by buttons or he's watching his favorite tv shows.

He loves things like jumping on trampoline, indoor playgrounds, slides or swimming.

One of the most issues beside the communication and intellectual impairment that we have is, that Luis puts almost everything in his mouth and much salivation. We also have problems with sleeping but since he is visiting the kindergarten we have the feeling that this is better now. He doesn't understand what is dangerous like driving cars on street or ponds where he thinks that he can jump in to swim . He's still wearing diapers, need help with eating, washing etc.

We have phases in Luis life, where he is crying for no reason for several weeks. Then we have days where he's happy for no reason also for several days.

Luis is currently in a inclusive kindergarten with group of 15 kids (5 with special needs), where he also gets speech and physical therapy. We have the feeling that he is really happy there.

Luis has no issues with locations where many peoples are, he is not aggressive or difficult.

We hope that we won't have regressions one day.

At the end we hope that we can get Luis as most as possible independent, for the day that his parents are not on this world anymore to take care.

We also hope that drug treatment are also possible in Germany one day.

Benedikt, father of a 34-year-old son living with PMS (submitted in both German and English)

Unser 34 jähriger Sohn mit PMD (Diagnose mit 29 Jahren) ist geistig schwer behindert und lebt in einer kleinen Heimeinrichtung. Seit seinem 13. Lebensjahr erhält er psychiatrische Medikamente, um Erregungsphasen mit Impulsspitzen zu dämpfen und herausforderndes Verhalten einzugrenzen. Er bekommt schon seit mehreren Jahren einen Mix aus einem

Stimmungsstabilisator (Lithium, derzeit Valproat) , einem Antipsychotikum (Quetiapin, derzeit Risperidon) und zusätzlich ein Sedidativum (Pipamperon) in wechselnder Dosierung. Hypertonie war bei ihm keine Problem, er hat als Kind sogar Fahrrad fahren gelernt.

Wir Eltern haben den Eindruck, dass die klassischen Medikamente beim Phelan-McDermid-Syndrom eine viel stärkere Nebenwirkung auf die Motorik und die Wahrnehmung haben, als die Psychiater dies normalerweise bei gegebener Dosierung erwarten. Bei unserem Sohn scheint es hier sogar Triggerschwellen zu geben, bei deren Überschreitung plötzlich drastische Störungen auftreten: Angst vor Treppen, starke Gangunsicherheit, Verlust der aktiven Sprache, Antriebslosigkeit, gefährliche Beeinträchtigung von Kauen und Schluckreflex. Beeinträchtigungen, die bei Reduktion der Medikamente bisher immer wieder zurückgehen. Daher sind wir sicher, dass die Medikamente hier eine grosse Rolle spielen.

Schon bei niedrigerer Dosierung unterhalb der Schwelle treten unkontrollierter Speichelfluss, Inkontinenz und starke motorische Unruhe mit ständigem Herumlaufen -als "normale" Nebenwirkungen- negativ in Erscheinung. Bei bedarfsweiser Erhöhung des Seditativums kommt zwanghaftes Essen und Trinken und als Problem hinzu. Diese Nebenwirkungen und "Dyskinesien" müssen wir Eltern leider akzeptieren, um den Heimplatz nicht zu gefährden.

Wir sind mit der medikamentösen Behandlung nicht zufrieden, weil sie nur Symptome behandelt, die aus Problemen mit der realen sozialen Umgebung resultieren. Sie macht den Patienten "sozial kompatibel", indem sie ihm aber körperliche und mentale Kompetenzen nimmt, ihn auf Dauer schädigt und zu einem Pflegefall macht.

Our 34-year-old son with PMD (diagnosed at age 29) is severely mentally disabled and lives in a small residential facility. He has been on psychiatric medications since age 13 to curb episodes of agitation with spikes in impulses and to limit challenging behavior. He has been on a mix of a mood stabilizer (lithium, currently valproate), an antipsychotic (quetiapine, currently risperidone) and also a sedative (pipamperone) in varying doses for several years. Hypertension was not a problem with him, he even learned to ride a bike as a child.

We parents have the impression that the classic medications in Phelan-McDermid syndrome have a much stronger side effect on motor function and cognition than psychiatrists normally expect at given dosages. In our son's case, there even seem to be trigger thresholds here, beyond which drastic disturbances suddenly occur: Fear of stairs, severe unsteadiness of gait, loss of active speech, listlessness, dangerous impairment of chewing and swallowing reflex. Impairments that so far always recede when the medication is reduced. Therefore, we are sure that the medication plays a big role here. He has been on psychiatric medications since age 13 to curb episodes of agitation with spikes in impulses and to limit challenging behavior. He has been on a mix of a mood stabilizer (lithium, currently valproate), an antipsychotic (quetiapine, currently risperidone) and also a sedative (pipamperone) in varying doses for several years. Hypertension was not a problem with him, he even learned to ride a bike as a child

Even at lower doses below the threshold, uncontrolled salivation, incontinence and strong motor restlessness with constant pacing -as "normal" side effects- appear negatively. When the sedative is increased as needed, compulsive eating and drinking and is added as a problem. Unfortunately, we parents have to accept these side effects and "dyskinesias" in order not to endanger the home place.

We are not satisfied with the drug treatment because it only treats symptoms resulting from problems with the real social environment. It makes the patient "socially compatible", but by taking away physical and mental competences, it damages him in the long run and makes him a nursing case.

Translated with www.DeepL.com/Translator (free version)

Nadège, mother of an 11-year-old daughter living with PMS

My daughter with PMS, Téhani is 11, diagnostic at 2 years. Symptoms with most impact is hypotonia this is everywhere in her body she walked that at 5 years old does not speak she only eats mixed. she had a lot of digestion problems from reflux and constipation (a little better regulated thanks to olive oil and tcm oil). hypotonia does not allow her to close her eyes completely and suddenly it is necessary to make her room completely dark so that she can sleep more (she has a secure bed because otherwise there is no notion of danger that she will flee). she also has socialization and communication problems, she has anxieties in closed places or outside if too many people. She cries at every stop in the car because she loves the car to drive. the hardest times are the stores with no patience waiting for you to choose the products and the worst at the checkout. Thanks to help us round treatment or gene therapy.

Carly, mother of a daughter living with PMS

Fears I have for the future:

- Regressions
- Her wandering at night and being able to climb over gates and get into danger
- Her getting bigger and more difficult to care for
- Her being at school and someone hurting her or not caring her the correct way
- What happens when I pass, its terrifying putting that on my other 2 older daughters

Maureen, mother of a five-year-old daughter living with PMS

My daughter will be five in February. She was diagnosed with Phelan-McDermid Syndrome at 21mos. It was devastating. The initial blow of the diagnosis and reading what that all entailed broke our hearts. We are very lucky that our daughter is happy and for the most part healthy, and as time goes on, the grief we felt becomes less and less. However, we still face many day-to-day hurdles, and I think one of the biggest is an inadequate means of communication. Our

daughter is non-verbal. She lacks the fine motor and cognitive ability to properly sign. We have begun to introduce an AEC device but We are still in the beginning stages. She's been in speech therapy since she was 22mos old with a large gap due to the pandemic. Progress is slow. I have to guess what she wants or what she needs. I have to read her moods, but I'm not always sure if I'm correct in my assumptions. 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. I know future drug therapies may not change this. Phelan-McDermid is a complex syndrome and the symptoms and the severity of those symptoms vary from person to person. I don't know if there can ever be a cure all. While I want a miracle, right now I'm surviving on hope. Hope that one day I'll hear my daughter's voice. I know it will be beautiful.

Adolfo, father of a child living with PMS

I know we as parents of a PMS child, we would like to get the cure for PMS, or a treatment to reduce symptoms to improve the future of the PMS children; BUT thinking as well of those family who don't have the resources for diagnosis is also quite important, so maybe as well to work on diagnosis as well as on treatment.

Please keep in mind the PMS is all over the world and lack of access for diagnosis somehow affects awareness and research.

Kristine, mother of a 22-year-old son living with PMS

Comment 1: Our son is on four different medications--depakote for mood stabilization, lorazepam for catatonia, anafranil for OCD, and clonidine for sleep. He is on daily dose of miraLAX for constipation. We have had to use enemas on many occasions. He takes Vitamin D daily. Prior to the age of 12, he took no medications. He received OT, Speech, and special education services starting at the age of 15 months through the age of 18. Antipsychotic meds cause his catatonia to worsen. SSRIs, if increased too quickly or to a certain point, cause mania. 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, tvs, 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. Our We have to cut all of his food into small bits and monitor him while eating as he overstuffs his mouth and chokes. He wears adult pull-ons as he can be incontinent and requires them for bowel movements. My husband is our son's full-time caregiver having had to leave employment to do so. 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.

Comment 2: Antipsychotic meds worsened symptoms. Lorazepam was a game changer.

Comment 3: A challenge is determining what the root cause of the behavior is--is it mania, catatonia, OCD, anxiety, GI pain, sensory issues/overstimulation leading to an autism meltdown, mood dysregulation that is causing the behavior?

Comment 4: Looking at the lifespan of our PMS child so far, it is incredible to think that his quality of life compared to the norm at the start of his life was poor but improved over the first 12 years of his life. And now the last ten years of his 22 years of life have seen a decrease in quality of life in ways I would never have imagined. It is vital that when treatments are considered for this syndrome, please please consider the changes that occur over the lifespan!

Teresa, mother of a 16-year-old daughter living with PMS

Comment 1: My daughter, Tallulah is 16 years old and was diagnosed with PMS at 5 months while in NICU after premature birth. Her father and I divorced when Tallulah was 4 years old and her brothers were 11 and 7.

Tallulah is verbal, joyful and works hard everyday to grow and maintain the skills and life we have helped her build. She has many manifestations of PMS; autism, IDD, GI impacts, hypotonia, hyper-mobile joints, hip dysplasia, scoliosis, lordosis, femoral anteversion, pain tolerance issues, lack of community safety awareness, etc. She also lives with Polycystic Ovary Syndrome and has an IUD to treat anovulatory bleeding, which began at 11 years of age. But, Anxiety is one of the most difficult and tricky aspects of this disorder for Tallu and for those who love and support her. Her anxiety coupled with the lack of understanding and sophistication of thought needed to logically navigate life's challenges and changes make life so hard for Tallulah some days. The thought that she might face the debilitating mental health episodes that are associated with PMS is terrifying for me. These tough mental health episodes as well as the stress of constant care, and hyper-vigilance have had a cumulative impact on my mental health. Elevated stress levels caused by Tallulah's symptoms and managing her world to date (and into the future) probably put me in a chronic PTSD subgroup.

This becomes a concern as we face the future. How will this constant stress impact my health? How will I be able to manage her care going forward? As we are faced daily with reports on the staggering deficits in supports, support staff, facilities, schools, teachers, healthcare options etc in the disability community, we as families will be caring for our loved ones indefinitely.....This is why it is so important to target therapies as soon as possible. We are, all of us, really standing at the edge of a precipice with no safety nets.

We need some relief across physical and mental health domains for our PMSers in order that WE have the strength to manage each day going forward.

Comment 2: Tallulah's socially driven personality, & willingness and ability to participate have made her constant involvement in therapies (since 8 months old) very successful. Especially oral-motor (prompt) 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.

In infancy, having her tonsils and adenoids removed and underlying dental issues taken care of surgically, improved her quality of life immeasurably. (ameliorated sleep issues, reflux, constant lung infection)

Keeping her on a Gluten-Free, Casien-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. -

We have been able to take her off MiraLAX by increasing water intake, removing constipating foods and introducing calm magnesium and prune juice.

Frances, mother of a five-year-old son living with PMS

My son Anders is 5 years old. He has PMS and is globally delayed. When he is healthy, he is a happy, interactive, busy boy that loves people.

We have been able to improve sleeping disturbances (awake all hours of the night) with clonidine and melatonin. We have been able to keep his seizures under control with Keppra. He has cyclical vomiting and we are currently unsure of the cause, it is stopped after the onset with medicine.

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.

He cannot feed himself (will overstuff his mouth and choke). He also does not chew effectively and must eat softer food as he often swallows food whole.

He learned to sit at 12 months, crawl at 18 months and walk at 4 years old but does not understand stairs or changes in elevation unless it is in an area where he has been hundreds of times to learn.

He also doesn’t have any awareness of danger, when he falls he doesn’t have the reflex to catch himself and falls like a tree. He has lost multiple teeth from falling. All doors in our home are child proofed, for example if he can get into the bathroom he will try to get into the bathtub, he has fallen into it on a few occasions.

He elopes, if he can open the door to get outside he would either fall down the steps to get out of the house or wander off with no awareness of where he is, who he is or the danger of traffic/strangers.

He is not toilet trained, he doesn't have self awareness at this level. He cannot dress himself, wash his body in the bath, brush his teeth, or any other self care things that most people take for granted.

Once we were able to get him sleeping through the night we have seen an improvement on his growth with social behaviors (crying, biting, anger/frustration outbursts), as a result he was able to attend special needs preschool.

Before starting school, he was asked to leave 3 different daycare's in 3 years for a combination of outbursts of anger/frustration, biting and crying uncontrollably for hours.

There are so many things I would love to see my son be able to do that I worry he never will. I am also terrified of him growing, he is 5 years old and is already 4' tall and weighs 60lbs. How will I care for him when he is bigger and stronger than me. I also worry about puberty and the possibility of regressions.

Marie, mother of a son living with PMS

My son is being treated with Diazepam, Baclofen for behavioral problems, psychiatric disorders dystonia. CBD oil is also part of treatment for anxiety and muscle relaxer approved by my son's doctors. My son also takes Belsomra (Suvorexant) for sleep. Belsomra works very well for my son. Baclofen and Diazepam are helping but we're hoping for better treatment in the future. Thank you.

Norma, mother of a daughter living with PMS

I would like to share with you my experience with My daughter Lorena. She was medicated with IGF 1 Increlex during 9 months and she had very good results, she improved in physical and mental skills, we stopped to make sure the improvements where 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, we went off because of Covid and Lorena's age, she was 16 and she stopped her growth.

Traci, mother of 21-year-old twin girls living with PMS

Comment 1: As our twins have gotten older the behavioral challenges have increased and aggression is sometimes seems to come out of nowhere impacts our ability to go and do anything. Also the aggression that can take place between our twins (21 years old).

Comment 2: Cognitive delay, regressions, neuropsychiatric challenges, aggression, anxiety, and OCD, limbic encephalopathy.

For Brookelyn on her best days: she is funny, witty, happy, and able to go to the bathroom without accidents. Worst days: she is crying, yelling, obsessing, clearing off cabinets, taking all the laundry and putting it in the laundry, both clean and dirty, removing everything from her closet, urinary accidents. During some of our most severe phrases, Brooke lost her ability to

communicate, feed herself, toileting. Since receiving IVIG every 3 weeks for the past 4 years she has not had that level of severity.

Alex best day: she is happy, creative, helpful, able to help with things around the house, increased independence. Worst days; seizures, severe OCD, urinary accidents, aggression, temperature dysregulation.

I would love for my girls to have more independence and an increased awareness of safety issues. I would love for them to be able to consistently enjoy daily activities and outings rather than the waxing and waning that comes with this disorder. We have day to day or even hour to hour changes that can be so unpredictable. I wish they could expand their topics of conversation, rather than obsessing over movies, and stuffed animals, and "stuck" on asking the same questions repeatedly.

They continue to obsess over things they care about and the perseveration has increased and they are often upset because they don't understand waiting. They don't an understanding of time. The aggression that occurs especially between Brooke and Alex is more concerning because they are grown and are stronger and can cause more harm to each other when upset. We continue to add medication and environmental changes to be proactive in preventing any injuries that they may inflect on the other one. They are remorseful after they calm down and realize they hurt their sister. However, the impulsivity and aggression is so challenging.

To manage the symptoms, we work with our pediatric neurologist, and psychiatrist and use medications to try to help manage the aggression and impulsivity. When they are at their worst we use Trazodone, Hydroxizine to help calm them. Worst case scenarios, we use Nayzilam to help calm them to reduce aggression and prevent them from causing physical harm to others. All under doctors guidance.

Both girls are receiving IVIG monthly which seems to have help them regain and maintain communication skills and cognition. We have yet to find anything to assist with the OCD, and anxiety. It is difficult to know the role hormones play in these changes as they are on continuous birth control, but still have breakthrough bleeding.

Heather, mother of a 13-year-old son living with PMS

Gavin, 13, is epileptic. He uses Lamictal to keep them at bay. But it also helps tremendously with his mood stabilization. This said, he does have FLAIR noted on his latest MRI.

Jose Ramon, father of a daughter living with PMS

Family-centered early developmental intervention is doing very well for our daughter. Family centered interventions are supported by evidence for treatment of a wide range of neurodevelopmental disorders.

Jaimie, mother of an eight-year-old son living with PMS

Comment 1: Our son Bodhi needs treatment to improve his cognitive quality of life. I think until there is a treatment to address the root cause of Phelan-McDermid Syndrome treatment options will be futile. We need a trial looking at treatment to improve the neuroplasticity of their brains and better communication between the synapses. If we have a better targeted drug, medication, gene therapy, etc. that targets the brain for PMS sufferers, symptom improvement will be seen in many areas. Better behavior, less mood swings, improved ability to learn, improved relationships, less stress on families.

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

Comment 2: We almost lost our son, Bodhi, shortly after birth to a congenital heart defect he was born with, Total Anomalous Pulmonary venous return and an atrial septal defect. He had open heart surgery at 9 weeks old and coded on the way to surgery. We didn't know at this time he had Phelan McDermid Syndrome and heart defects are caused by this deletion.

Bodhi has faced insurmountable challenges in his short 8 years of life. After years of speech, OT, and PT therapies to gain motor skills, learn how to eat solid foods, build language skills, balance, and sensory input he faced a major regression at 2 years old. He completely lost the ability to speak after having upwards of 50-75 words and began having major balance issues running into walls walking, falling when running, etc. This was devastating for him and us, and the world he communicated with around him. Frustration and behaviors were occurring as he could no longer communicate his wants and needs, along with mobility and safety challenges walking.

After many continued years of therapy, stem cell treatment in Panama, and adding Avmacol and phosphatidyl choline daily he began to regain the ability to speak at 6 years old and better proprioception/balance. Honestly we live in fear we may lose him again to regression at any time in his life course as we have learned how common it is in PMS. Sometimes those hard-earned skills are lost forever. No child should have to suffer through this or families.

There are many difficulties in PMS, ranging from health complications, difficult behaviors, mood swings, and moderate/major intellectual disabilities. Impacts on the individual, families, and siblings are huge, adding stress with no treatment available for those having PMS. My heart gains hope in your reading this you may be able to offer the treatment that Bodhi and every person impacted by this devastating syndrome deserves. One that offers a better quality of life and improved health. One that offers a better future and outcome for our kids.

Samantha, mother of a seven-year-old son living with PMS

Reflux - my son Camden (7 years old) has been on some sort of reflux medicine since birth. Currently on Esomeprazole 2x a day. Doctors seem at a loss at this point. Working on getting a 3rd opinion.

Maureen M., mother of a daughter in her 30s, living with PMS

Most difficult in the long run, has been her regression starting at age 5. It was devastating.

Now that she is in her 30's, managing her symptoms of anxiety, sleeplessness, crying unpredictably and then bouts of periodic screaming is very difficult. She is bi-polar. She has periods of calmness and then extreme anxiety. She cannot sleep at this time.

She has nothing that's engages her, except food!

Linda, mother of a 22-year-old son living with PMS

Electroconvulsive therapy has been an essential component of treatment for our 22-year-old son's agitated catatonia.

I think that neuropsychiatric issues are underrepresented in the overall discussion, perhaps because of the demographic of participants. (These issues typically first appearing in later teen years.) Psychiatric issues can be absolutely devastating to the PMS individual and caregivers.

Cristina, mother of a 44-year-old son living with PMS

Have been undiagnosed until 2022. My son is 44 now and have been on Clozapine for 25 years after an episode of Catatonia. He was diagnosed as schizophrenia as diagnosis of choice.

Other than that, his main disability has been language development which has affected his ability to interact socially and get a job which he really wants.

He has mild bipolar and a bit of OCD which started after a few years on Clozapine.

Victoria, mother of a 10-year-old daughter living with PMS

This has been such a wonderful event, I'm so pleased I've joined you. My daughter Emily is 10 and has PMS she is an absolute joy to be around, but I'd love to know if there would be a treatment to help with communication in the future. Knowing her thoughts would help me hugely.

Michelle, mother of a child living with PMS

In looking to the future- I hope we have better treatments to treat &/or stop regression. Our kids & families deserve to have the best life possible. Watching regression is so heartbreaking.

Erica, mother of a son living with PMS

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.

Chris, parent of a child living with PMS

Improved communication and cognition would be game changing. As was mentioned, our kids seem to understand a lot more than they can communicate. How can we find the best ways to measure improvement in clinical studies as many endpoints rely on verbal or traditional measurements?

Melanie, mother of an adult child living with PMS

Treatments for the neuropsychiatric issues that work and don't make things worse are priority for me. My child went from mild developmental delay with very good speech and able to write, read, do independent self care etc to after puberty and a viral illness waking up one day as a totally different teenager unable to speak etc. Took two years for accurate catatonia diagnosis and till late twenties for the PMS diagnosis.

Cyra, parent of a child living with PMS

With regards to future treatments- we would love for unconventional therapies like Rapid Prompt Method and Spell 2 Communicate to be researched more. Both of these therapies utilize letter boards and gross motor skills to point or poke letters and spell words. Several PMS children have shown, somewhat miraculously, that they are able to communicate highly intelligent, age-appropriate messages via these methods. Unfortunately, RPM and S2C are not favorably recognized by certain organizations at this time but some of the results are nothing short of amazing. Demand is very high and trained therapists are hard to come by right now but, if trials are favorable, perhaps more non-speakers could have a viable means to communicate wants and needs.

Diana, parent of a child living with PMS

Often overlooked are hormones (endocrine system) for all PMS individuals as puberty seems to exacerbate some symptoms and women's health issues including polycystic ovaries.

Navi, parent of 25-year-old son living with PMS

My Sahib got diagnosed at age 22. He is now 25 years old.

We dealt with regression at age 6 when he lost his speech and other skills, it never came back. At age 9 he became very aggressive, maximum sleep was 2-3 hours a night regardless of medication. All the meds psychiatrist, neurologist and paediatrician were trying he was doing opposite of what that medicine was supposed to do. Age 16 his Integrative GP did a test to check his tolerance against Meds like Resperidal, temazepam, Avanza, etc.. he was on. He then suggested to wean him off slowly and see what happens. We were pleasantly surprised to see him getting better.

His Catatonia was at its worse at age 18. None of the doctors knew that it was catatonia as he was scared of going through doorways, exits and was scared to cross boundaries. I have videos I

can provide. It was the same time when he graduated from high school for special needs. He was diagnosed with Smith-Magenis syndrome by mistake that time. But after couple of years trying to see how he fits in that syndrome, I couldn't find any similar symptoms. So requested the genetics in his hospital to check again. Doctor agreed and this time he got diagnosed with PMS and it all made sense and answered all our "why's". Why he reacted to those antipsychotics, why he lost his speech, why he has extreme gut issues.

Currently we are struggling with

- Catatonia in different form
- Classical and excited
- Bipolar- Mania is extremely hard to manage.
- Aggressive behaviour due to frustration he deals with.
- Acute Gut issues, inflammation. Constipation, reflux, Blood and protein in urine. All test conducted by Kidney specialists, urologist come back negative. He suffers with pain IN STOMACH even though he has high pain resistant.
- PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection)

CATATONIA AND MANIA are too hard to treat as medication is limited and Doctors are not aware of different forms of catatonia in my country.

Monica, mother of an 8-year-old daughter living with PMS

The main problem with my 8-year-old daughter are severe neuropsychiatric disorders- SIB, OCD, ADHD, anger about everything, mood disorders, crying or euphoric behavior, laughter for no reason.

I suffer from depression. I cannot cope with my daughter's self-harm.

We are excluded from social life. screaming and self-aggressive behavior as well as a lack of concentration exclude the daughter from school education as well.

My daughter has been taking lithium carbonicum for 6 weeks but without any minimal positive symptoms.

2 years ago Risperidon also without positive effects.

I don't know what drug I could try now to soothe her anger and aggression.

My daughter has also been attending SI therapy for 6 years and in the past - rehabilitation

Mary B., mother of a daughter living with PMS (variant)

Hello, my daughter was diagnosed at the age of 3 with a PMS variant. As a first-time parent I didn't know what to expect, but everything seemed normal. She seemed so strong healthy and happy made eye contact tried to talk very vocal crawled and walked on time but I did always

notice something seemed off about her neck and she would always sit with a lean. Doctors didn't seemed to worried about it I noticed this lean never went away and her neck muscles and control balance was weak but by age two she started not making eye contact stopped being vocal lost interest in things and sometimes wouldn't respond to sound we got her hearing checked and everything was ok, cause when it was a sound mostly a song she would look.

She also had a lot of chewing problems due to low muscle tone we had to do a minced diet or baby food. Graciee finally at 2 was diagnosed with autism and got ABA it helped Gracie sooo much. She makes eye contact and can communicate through pecs and is working on a communication device from speech therapy. Gracie is so much more curious about engaging in activities she's is thriving and learning new things everyday now. Gracie can chew and eat almost everything but hard candies. She is more aware of surroundings and watches where she is walking Gracie is now a sensor seeker and loves swimming and kinetic sand play dough and slime. Gracie loves to just snuggle up and listen to songs on her iPad. Gracie is high maintenance and loves a daily massage. Starting her ABA school has also helped Gracie get a regular sleep schedule. She use to really struggle with sleep. I hope Gracie can continue to be successful and continue growing and glowing. She inspires me everyday and taught me so much. She is my greatest gift and blessings. I'm so lucky to be Gracie's Mom.

Ramkumar, parent of a 15-month-old son living with PMS

My son is 15 months old, diagnosed with PMS.

Losing skills that my he learned previously, delayed development, and low muscle tone. These are some of the symptoms that impact my son's life a lot.

On the best days, when he is happy, we can take care of him well, but when he isn't feeling well, he can't communicate with us, making us feel helpless. Sometimes he cries, but none of us can identify the cause no matter what we try.

We would love for him to communicate, move, sit, etc. Right now, he is not crawling or walking at all. Also, we would like to have him toilet trained. Acquiring these skills will help with his quality of life as he grows. Needless to say, it will allow us to care for him easier too.

On average, as he becomes more aware of his surrounding people and kids like him, he seems distressed for some reason. Of course, it could be sensory overload.

Therapy and lot of cuddles, and playing his favorite music are what we currently do to help him manage the symptoms.

I do believe the discussed treatments will help him gain some of these skills I talked about. This will be literally a life saving option for my child and all of us.

Jason, father of a 14-year-old son living with PMS

I wanted to document the danger and difficulty in coordinating care and medications between doctors.

Drew (14 year old - NYC - PMS) was prescribed clonidine by his neurologist to address some minor yet concerning behavioral issues. Unbeknownst to us, clonidine has an uncommon yet dangerous side effect of contracting the bladder neck, which causes urine backup. Drew like many in the PMS community has had kidney issues since birth (bilateral hydronephrosis).

We were hesitant on starting Drew on any meds as he is non-verbal and cannot communicate any issues that he may experience from the meds.

Shortly after starting the clonidine, Drew stopped urinating, causing a very dangerous condition. Numerous visits to various specialists, numerous invasive tests and countless conferences with his medical team could not figure out the cause of the backup.

By chance, a family friend (studying to be a nurse) suggested we look up all his meds to identify any potential side effects.

Low and behold, clonidine has a largely unknown side effect of bladder neck contraction...none of the docters were aware, nor considered that a possible cause when initially prescribing and we were told that it is a common and harmless drug which is regularly prescribed to autistic and special needs children, even in anticipation of possible issues. This almost care-free attitude towards a traditionally 'safe' medication, caused months of issues with Drew....

The variety of non-related issues found in PMS kids makes it a challenge to treat them pharmaceutically without exacerbating possible dangers and issues with their other PMS symptoms...

Thankfully, we as parents, with the advice of a nursing student friend, were able to identify and address the cause while over a dozen specialists from NYU Langone and Mt Sinai hospital had no clue. It could have been a medical disaster.

Amanda, mother of a daughter living with PMS

My daughter suffers from pica. While it comes and goes in waves with some of the other behaviors that she suffers from, when it’s bad it is very scary. During these times, she puts everything in her mouth and doesn’t have the motor planning to get it out if it’s too small or a piece breaks off. It poses a huge choking risk.

She also suffers from body temperature regulation. Her body can’t regulate on its own and she is at a huge risk for easily over heating in our hot California summers. While we have a cooling vest, she can’t be out with it for more than 30 mins or so.

Lastly, she had a regression early on in her life. She was hitting most milestones at the tail end of development but her the babbling she had completely left and didn’t come back for 1.5

years. She didn't even really make sounds didn't that time. We've seen other regressions like making progress in toilet training and losing it all.

Catherine, mother of a daughter living with PMS

The three symptoms that have the most significant impact on our daughter's life are: seizures, kidney function and constant chewing - on everything!

Kathleen

Mitochondrial. It effects alot of things, that are looked at specifically. But overall I think mitochondrial dysfunction is just overlooked. If mitochondrial issues are addressed I believe some of the other issues also are addressed.

Nora, mother of a 14-year-old son living with PMS

Unlike most of the PMS community, my son Carlos age 14, is super strong, he can walk on his own, non-verbal, still in a diaper cognitive he is about 3 years old. Has aggressive behavior but mainly self injures and headbutts my house walls making holes in them, doesn't sleep all night. Suffers chronic constipation

Anxiety and the list goes on. We are physically mentally and emotionally exhausted but placing him in a home is out of the question. We hope you can find some way of helping the PMS community. May God bless you and guide you to the answer/cure for PMS.

Jessica, mother of a 14-year-old son living with PMS

My son Alexander is now 14 years old, non-verbal and still wears diapers. We are blessed that he walks however he still needs assistance with all daily tasks. 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. A chewy tube helps to alleviate this behavior but does not detour him from doing it.

Alexander also has renal-reflux and had corrective surgery in 2021. He does not experience any UTIs. We discovered this when he was 4 when doing a routine examine requested by his geneticist who wanted to have him all checked- heart, kidneys etc.

During Alexander's early years (3-10) he was in and out of the hospital due to pneumonia. Overall, Alexander has become healthier and other than the sleep issues we haven't experienced health issues in the last few years.

Erin, mother of an 11-year-old son living with PMS (5.2mb interstitial deletion not including *SHANK3*)

Gideon is 11. He had hypotonia from birth, but didn't get his genetic testing until just before 2 years old. He has a 5.2mb interstitial deletion not including SHANK3. For him three of the biggest concerns are his low muscle tone, lymphedema and social/emotional struggles.

The low muscle tone means he can't do several things his younger brother and sisters can do like monkey bars, walk for long distances, jump rope, participate in team sports and so much more. He has parks he cries if we go to because there are too many monkey bars and everyone can do them except him. He has a wheelchair we use to go to zoos or other attractions where there is significant walking. He gets worn out so quickly in sports like basketball or soccer, so

now he doesn't even want to try. No one passes the ball to him anyway. It's heartbreaking to see him want to do the things all the other kids around him are doing, and yet he can't.

Lymphedema is the other big concern for us both for now and the future. It has caused cellulitis twice now. The last time was in the spring in his ankle. He had to visit the pediatrician 3 times in one week to make sure the infection was truly going away and he didn't need IV antibiotics instead of the oral ones. He missed a lot of school that week. Since that point, he got leg compression pumps. They worked wonderfully all summer! His feet looked like normal feet! But once he started back at school, sitting at a desk so much of the day, his feet are puffy even after the hour of the leg pumps. I don't know what else to do since the few times he tried compression socks, he got athletes foot for 2 weeks. His feet sweat non-stop.

Emotionally he is immature. He will cry for 30 minutes over not getting to play a certain game. He takes 3 stuffed animals to school everyday, and he's in general education 5th grade. He struggles with friendships.

Natasha, mother of a five-year-old daughter living with PMS

While PMS affects Delaina (5) in many different ways, the top 3 symptoms the affect her every day life would probably be non-verbal, body temperature regulation, and inner ear problems. Delaina has also been diagnosed with ASD, PICA, hypotonia, and incontinence. Currently she is in therapies through her public school and in the special needs classroom. On our best days, Delaina is pretty much just like her peers. On our worst days, Delaina is eloping, messing with everything in sight, and sometimes irritable.

Marko, father of a 16-month-old daughter living with PMS (4.58 kb *SHANK3* deletion)

My daughter name is Tara. She's 16 months old.

She has 4.58 kb (yeah...that small) deletion of SHANK3 gene (arf|GRCh38] 22q13.33 (50694375_50698957)x1 dn).

With that she also has hypoplasia of corpus callosum.

To answer your questions:

1. The most significant impact on our lives are:

- the inability for Tara to express her feeling towards us (she can't speak) - not being able to tell us if something hurts is a very serious problem.

- she has mental or neural development lag (she still doesn't walk or even sits)

- she seems to forget the skills she learns over time...which is very sad and frustrating.

2. The best days are when everything goes the same. Same ol' day with same ol' workout and feeding routines. The worst day is when she cries all the time, doesn't sleep (or sleeps maybe 1h during the day or maybe 4h during the night).

3. We would like (for now) for her to start walking or even sitting on her own. Even holding the spoon and realizing it is a spoon would be a milestone.

4. Me and my wife are trying to stay positive but it is hard! Seeing other people's children (who are normal) is getting to us on a deeper level. We are focusing on today and that's it. Not planning tomorrow is the key to staying positive.

5. We are doing the work with Tara! She has her physical and cognitive exercise done regularly and she is slowly (snail slow) advancing. We are exploring every option we can for her to advance in development. Since she's only 16 months old we are limited.

6. There are no treatments! What we are doing is simply trying to get the best of what we have. We are hoping (hope is what dies last) for the miracle cure or any genetic treatment but we know that when this treatment does come it will be for the newly born children and not for our Tara.

Hope this helps in any way.

Rachel, mother of a daughter living with PMS

Of all symptoms of Phelan-McDermid Syndrome, which 1-3 symptoms have the most significant impact on you and your loved ones life?

Sleep disturbance, repetitive sensory seeking behaviours and symptoms of mania such as if she is driven like a motor 24/7, with over-the-top levels of energy and activity. It is difficult to maintain energy for carers when we are needing to get up for the day at 2am or having limited sleep. This is despite medication management. She wakes up many times during the night and takes hours to be resettled. During the daytime and night, she displays repetitive sensory seeking behaviours and needs to be redirected from things such as the tap, water, the fridge, doors etc. Part of the difficulty with sensory seeking behaviours is they are repetitive, and she has a low perception of pain. These repetitive sensory seeking behaviours can cause injury which she does not recognise. This also goes hand in hand with mania. She has a lot of energy and activity, which is never ending. As she doesn't have a stop button, she requires 1:1 supervision (sometimes 2:1) 24/7.

How does Phelan McDermid syndrome affect you or your loved one on best and on worst days? Describe your best days and your worst days.

She requires assistance with all of her daily living and personal care tasks including eating, showering, toileting, brushing teeth, mobilising, accessing the community safely without absconding, reducing and redirecting from repetitive and sensory seeking behaviours. This applies when she is having a good or bad day. She goes to school from 9-2 on weekdays which

allows her to learn in a supported unit. She currently has support from behavioural therapists, physiotherapists and occupational therapists. When she is having a bad day, she requires 2:1 support to redirect her, prevent her from harming herself, manage symptoms of mania and supervise her 24/7 including during the night when she doesn't sleep. This places a lot of stress on our family as we need to organise carers, manage all areas of her disability and health care needs and focus on being parents and fostering our own relationship. Bad days can lead to parents not having sleep, eating properly and suffering from extreme stress leading to physical and emotional burnout. On good days, we enjoy spending time as a family and with the support of carers to play in water – which our daughter loves, going to the zoo, spending time in our swim spa and trying to have family time despite managing health and disability needs, and mitigating risk so she can stay safe and live her life to the fullest.

Are there any specific activities that are important that you or your loved one cannot do at all or as fully as you would like because of Phelan-McDermid syndrome?

Almost all activities are restricted. Schooling requires adjustments and a supported placement with teachers aids, hypotonia reduces ability to engage in activities such as horse riding, swimming or any activity requiring muscle control. Difficulties with social skills reduces ability to engage with other children and an ability to understand safety and sensory seeking behaviours increases risk when entering the community. All activities need to be modified due to Phelan-McDermid Syndrome.

What are you currently doing to manage your loved one's PMS symptoms?

We have carers in the morning, afternoon and overnight to enable capacity building in all daily living and personal care areas, give respite and provide additional support in the home and community. We have a behavioural support practitioner who has implemented a plan which ensures safety and consistency across all stakeholders, family, carers and the school. We have a physiotherapist that helps with continence management and assisting her to improve her toileting habits, and to increase her proprioception and hypotonia. This will also improve her ability to walk and complete other daily and personal living tasks. She also sees an Occupational Therapist which assists in prescribing assistive technology to increase independence and assesses her functional capacity. She sees a paediatrician to manage her health-related difficulties including sleep, bowel difficulties and mania.

How well do these treatments address the most significant symptoms and health effects of PMS?

Medication partially manages sleep disturbance and recently sleep has improved, however she still has a lot of bowel discomfort, constipation, and bloating, despite medication and mania like behaviour. Behavioural therapists have helped with implementing redirection techniques to eliminate repetition of sensory seeking behaviours; however, redirections sometimes don't work or work better with specific people. Carers help with giving family respite from providing 24/7 supervision.

David and Maryjane, parents of a 31-year-old daughter living with PMS

Our daughter Maribeth (31 yo) began experiencing changes in behavior at the age of 26. There are days where she is extremely agitated/uncomfortable, to the point of aggression at times. Other days, she is sweet, loving and is able to participate in activities of daily living. It affects her ability to attend her Day Program on a daily basis, as well as social activities outside of the house.

We have found what we think is a direct correlation with GI issues and behavior. Often times, she has difficulty establishing a regular bowel routine, suffers from gas and is bloated. This seems to exacerbate her state of agitation. When she completely empties her bowels, there is an immediate calmness that comes over her. We struggle daily with trying to administer the right amount of MiraLAX and exercise, as well as eating a diet high in fiber.

So in summary, behavior and GI issues are the two areas that impact our lives the most. Thank you for your interest in helping our kids.

Michell, parent of a son living with PMS

I don't know how to distinguish our son's health and autism conditions, behaviors etc. from PMS. We deal with seizures, GI issues, sleep issues, bouts of non-stop yelling, pacing, elopement, mouthing non-food items, toileting and on. We had serious regression at age 6. Every aspect of lives are affected. We don't know what next steps to take.

Arseniq, parent of a son living with PMS

I want to tell you about a story and my point of view about the states and events of deletion of *Shank3* on my child. At an early age I realized that something was wrong about 2-3 years of age lagged with speech compared to the other children but slowly progress I had hopes I had hopes He would succeed, with a little, he liked to paint, to listen to the tales in this period in the kindergarten he was taking Carbamazepine because he was an active and fast child of these medications was drowsy and dizzy took them in a period of 3-4 years after the observer Neurologist prescribed Hydroxyzine Hydrochloride with this medical event no strength had no strength. The doctor was prescribed AdLiguid Brain Booster with the intake of these vitamins he regained his speech and active physical Skills mostly loved the noise of cutters, loving to deal with wood ordering with their splitting, had a period in which he slept with the ax and walked with her everywhere. Do you imagine people from countries? We walked in the woods and rode the horses with which Darbars drove the wood in rain and snow in the heat and the time he did not influence him was always happy and joyful did not get sick. This was already at first-class school age wrote letters of numbers but onwards 2'3'4 We lost interest in music, physical, painting and help teachers psychologist, speech therapist throughout the training period of 10 years to this day I am with him constantly and. here in Bulgaria, the parents are with the children at school, they are present in the lessons if the child wants, the parent takes him to the toilet, feeds him, takes him out of the lesson and accompanies him continuously. My child is in

a mainstream school with normal children, not in a specialized school because there is none in the city. Everything a child hears and sees is imprinted in his memory, every learned word, every action, the people he has seen, he remembers, he may not say when you ask him, but after a year or two, if you ask him, he will tell you. 80% of these children are affected by the environment, people, habits, lifestyle and 20% the lack of the deletion in *Shank3*. Naturally, the *SHANK* family is diverse and specific, but as parents, we will always see the best in our children and less of the disease, no matter how big it is. And here comes the scariest period for me and my son. The visit to the wrong psychiatrist, which I sought because he was entering puberty and because of his great excitement. The psychiatrist prescribed us the medication risperidone, the child started to score whole nights, for several days he did not sleep, he was even more overexcited he did not stop at one place, then the psychiatrist prescribed him olanzapine, the same thing, the child was getting worse, we went to another psychiatrist, he prescribed Aripiprazole from this medicine, the child was completely drugged, he could not hold his head straight, his eyes were constantly closing day and night. I told myself what is going on, something is wrong. I went to another Psychiatrist and explained everything and she advised me to do a pharmacogenetic test. We stopped all medications until the results of the test. Naturally, the results showed that these medications for the child prescribed by the psychiatrists had side effects, increased attention, narcotics. I did a lot of damage to my child trying to help him. Then we did the full exome sequencing and here we are now. Right now my child he doesn't take any medication he is very well calm, he sleeps, he eats, we walk we play we go to school not regularly, he gets dressed I am teaching him to talk again because with these meds he started making only sounds like animals. there is progress little by little we will succeed. But we learned the most important life lesson.

Miriam, mother of a six-year-old son living with PMS

My son developed typically until approximately 2 years of age. He met all his motor milestones on the early side of expected age. He rolled over at 3 months, crawled, then walked at 11 months. He played with his brother, he pretend played with toys, he imitated his brother and myself & my husband. He waved goodbye. He opened and closed doors. He tried on shoes. He made age-appropriate jigsaws. He followed instructions - put that in the laundry, put that in the bin etc. He interacted so well with us and was always full of fun. He self settled at night and slept very well. He was only delayed in speech (8 words at age 2 which progressed to 20 words).

Sometime after this my son regressed. He lost all his words, he lost his fine motor skills, he could not imitate, he could not wave goodbye (and still cannot at age 6). He did not play anymore with his brother. He lost attention skills and stopped playing with toys. He became dysregulated. He found it very difficult to hold a spoon and feed himself (he still does). His gross motor skills have remained intact and he has excellent balance and agility. He is full of energy and walks up to 5 hours per day.

Over the past 2 years after being a great sleeper, his sleep has become broken with early wakings.

He was diagnosed with focal epilepsy at age 4 and Phelan McDermid at age 5.

Valerie, mother of a 10-year-old daughter living with PMS

My 10-year-old daughter has Phelan McDermid syndrome, diagnosed in New York when she was 3 years old. We are a French/English family now living in Geneva, Switzerland.

She has severe gastro-intestinal issues, all her life revolves around how much pain she has linked to gastro issues everyday day. As a result, she sleeps very little and is up most of the night one out of 2 or 3 nights. This lack of sleep has a significant impact on our family life, with my husband not working for 7 years now due to his sleep deprivation alongside our daughter. She is also totally non-verbal and unable to communicate which makes understanding where she hurts, very complicated.

PMS impacts our daily life as one of the parent (husband) can not work, impacting the whole family budget. It impacts her brother and sister to see her in pain, crying, without being able to alleviate her pain. Due to her gastro issues, it is very painful for her to be seating in a car. Despite all the possible seating arrangements, it still hurts her, which in turn impacts our family life as it limits going out of the house as a family.

Because of her everyday being in pain - to a different degree - and sleepless nights, we struggle to have a normal family life, going out to do activities or having fun as a family, and due to her inability to travel by car.

Resilience is what characterizes our family, both our daughter with PMS and her siblings and us parents. We never know what the day will be made of, how much pain she will have today, if she'll have to be taken to the hospital if she'll be able to go to school.

My husband and I are devoting our lives to making our daughter less in pain and have the happiest life she can. My husband is with her most of the day and night, except when she manages to go to school (specialized school for disabled kids). When she hurts, we try to give her pain relief, or other medicines we have - most of the time that don't help, give her baths, and massages, and try to help her relax.

No treatment has yet been able to stop her stomach from aching nor allowed her to sleep at night when she hurts.

For us, addressing the multiple severe gastro issues that our daughter has is key and we would hope that research would be able to understand more and provide treatments. Addressing sleep issues would be equally critical for her and our family all together. We also believe that gene therapy would be great, being able to replace shank3 functions would clearly have an overall beneficial effect on her. She would then also be able to speak or communicate which would also change much of her life.

I would like to take this opportunity to thank you for all the work you are conducting at CureShank, thank you for integrating non-US based families. We remain available to extend

anything to Geneva Switzerland or put you in touch with doctors here, if and as needed. We also believe that research and gene therapy is essential.

Thank you again for all you do for our PMS children around the world and we look forward to continuing being in touch with CureShank.

Stephanie, mother of a daughter living with PMS

Comment 1: *Of all the symptoms pf PMS, which 1-3 symptoms have the most significant impact on you or your loved one's life?*

Absence of speech, intellectual disability and sleep issues are, combined, having the worst effect on each other and having the most significant impact on our family. When our daughter was younger, lack of sleep didn't seem to have any impact on her daily energy nor behavior. Now that she's a teenager, we see inappropriate behavior during the day when she didn't sleep through the night. Because of the intellectual disability, when our daughter wakes up at night, she doesn't read a book or watch the tv by herself until she falls back asleep, so someone must be with her at all times and her behavior sometimes even wakes up the whole family. We must make sure she doesn't wander in the house, doesn't try to leave the house, doesn't turn on the taps/faucets... This has a high impact on everyone's health and daily life. Not being able to express her needs, desires, emotions or pain, our daughter sometimes shows inappropriate behavior, doesn't always receive the full health care she should be receiving as well as it also doesn't allow some assessments to be made properly: the profound intellectual disability diagnosis might not be the most accurate, but the autism assessment cannot be performed because of the lack of speech... Interventions intended for people with an autism diagnosis might be best suited but our daughter's teacher and aides are better versed with people with profound intellectual disability.

Comment 2: *How does Phelan-McDermid syndrome affect you or your loved one on best and on worst days? Describe your best days and your worst days.*

On a great day, our daughter is calm, all smiles, cuddly, we play games together, go outside for a walk or fresh air, run errands, or participate in community activities and get to have heartwarming conversations with strangers. One of the worst moments of our daughter's life was when she had a cavity and we had to wait for 6 months afterwards for the surgery. Because of her intellectual disability she doesn't fully cooperate during dental treatments she has to be sedated. During this 6-month period, our daughter's behavior slowly became more and more inappropriate. She started pinching, slapping, crying for no apparent reason, not being able to wait during transitions. She wasn't herself. She couldn't tell it was her teeth hurting but we could. We advocated for her. Made an appointment with the dentist. Because there was no infection and no abscess, he could not more her on top of the waiting list. We ended up at the hospital because she started to wake up at night multiple times, apparently in pain, but medicine wasn't helping her. We were discharge with an anxiety hypothesis. A month later, she finally had her dental surgery and she immediately after seems to be doing better.

Her tooth wasn't formed properly, was shallow and fell apart as soon as the dentist tried to clean it. He had to remove it. Since that day, she came back to her joyful self.

Comment 3: *Are there specific activities that are important that you or your loved one cannot do at all or as fully as you would like because of Phelan-McDermid syndrome?*

As a family, we don't travel and don't do much of summer vacations all together (we split the family to allow the siblings to travel or to have summer vacations with one of the parents for example). We don't fully participate in family gatherings because our relatives and friends' houses are not proofed to our daughter's level of curiosity and intelligence in getting what she wants. We feel safe going to only some specific friends and family members that are fully receptive of our daughter's needs. Community activities, leisure, sports and cultural outings are not always possible and, if we do try to participate, we often end up attending for a shorter period of time when our daughter is with us. For the adults to be out with the kids, it takes a lot of organization and because we are too exhausted, we often choose to stay home and catch some sleep. When we do get out, it's usually one of the parents with one or more friends while the other parent stays home to look after our daughter.

Comment 4: *How has your loved one's ability to cope with the symptoms changed over time?*

I'm not sure our daughter's ability to cope with the syndrome improved nor exists. I might be wrong! She doesn't have the reflex to protect herself when she falls and doesn't understand that this is related to the syndrome she has. She doesn't understand that she has a syndrome and that there are symptoms related to it. She doesn't see the difference between her classmates (with various symptoms) and other kids she meets at the playground: they are all kids to her, and she enjoys their presence! Whenever she has a health problem, we take care of it for her, she doesn't relate it to her syndrome and just goes on with her life as much as her energy allows it.

Comment 5: *What are you currently doing to manage your loved one's PMS symptoms?*

There's medication for acid reflux, respiratory problems (when needed) and mostly for sleep problems. For communication, she uses a few signs (3-4), school uses pictograms for routine and requests, we use some pictograms at home too and Time Timer to help give some references with the routine, transitions and wait times. Many activities help maintain and improve our daughter's gross and fine motor skills, as well as her general health. There are medical follow-ups with many specialists (pediatrician, ENT, dentist, ophthalmologist, orthoptist, neurologist [to make sure we don't miss emergence of seizure activity], nurse) and many therapists involved to make assessments and update them when needed (occupational therapist, physiotherapist, psychoeducator, speech therapist, social worker, I might be missing someone!).

Comment 6: *How well do these treatments address the most significant symptoms and health effects of PMS?*

The only medication we keep adjusting is the one for sleeping problems. It is a recurrent problem, sleep issues come in cycles. At 13 years old, we finally have a combo that has been working for a few months… until it is not working anymore. So, the treatment is correctly addressing the symptoms, currently. As for behavior, the teenage years brought new behaviors we are still in a trial-and-error phase so I cannot say that the treatment (the interventions to stop the inappropriate behaviors) is not well addressing the symptom. The same applies for the lack of speech because we are still trying to find the right (improved or updated) method to allow our daughter to better communicate her needs, which should also address most of the inappropriate behaviors.

Sheri, mother of a daughter living with PMS

There a few challenges that stand out regarding my daughter with Phelan McDermid Syndrome.

She had a significant regression at age 13, experienced psychosis and lost many skills. She requires full time supervision. She puts non food items in her mouth and does not recognize safety hazards etc.

She also is incredibly strong - redirecting her can be physically challenging bc of her enormous strength. There have been times since her regression that it's taken 3-5 people to help her get up off the ground or to start an iv.

Another thing that's hard is the side effects that some of the meds she has tried have. For example, a medication might help in some ways, but that same med might also adversely contribute to her existing bowel and bladder issues, thus making her more uncomfortable.

Since her regression, my daughter has not been able to articulate how she feels. It's very hard to see her uncomfortable and in pain and have to guess what is hurting her and how to help her.

In addition to PMS, my daughter was also diagnosed with autoimmune encephalitis. She has been receiving infusions of IVIg and Solumedrol every 4-8 weeks for several years for her autoimmune encephalitis. I believe these infusions have a positive impact in regard to Phelan McDermid Syndrome as well.

These infusions help her a great deal and have been a game changer for us. She has become far more coordinated, has less OCD, in general sleeps better, her toileting skills are improved (while she requires assistance, unlike prior to her regression when she could use the toilet completely independently, she is able to void using the toilet easier). My child is a young adult and we have found keeping her IVIg/ Solumedrol infusions consistent to be very helpful. When we have pushed out her infusions, we see all kinds of declines.

I also believe these infusions along with Ativan help lessen my daughter's catatonia, but it never completely goes away.

Catatonia is also a challenging aspect of this illness. My daughter experiences both akinetic catatonia and excited catatonia.

I yearn for the day that there is viable treatment for Phelan McDermid Syndrome. My family along, with maybe others, have been greatly impacted. My heart breaks for the families who have lost a loved one from this illness as well.