GM1 Gangliosidosis
Externally Led Patient-Focused Drug Development Meeting
Voice of the Patient Report

Meeting Date: 14 October 2022

Meeting hosted by: Cure GM1 Foundation

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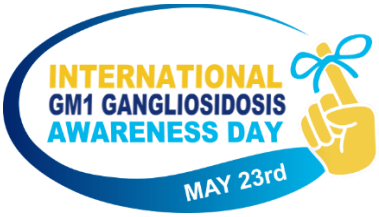

GM1 Gangliosidosis Voice of the Patient Report

The Cure GM1 Foundation's mission is to help support the drug development process, to fund GM1 research, and to help support the global GM1 community. This *Voice of the Patient* report was prepared on behalf of Cure GM1 Foundation as a summary of the input shared by families and caregivers living with GM1 gangliosidosis during an Externally-Led Patient Focused Drug Development (EL-PFDD) meeting, conducted virtually on October 14, 2022.

Authors and Collaborators: This report was prepared and submitted on behalf of Cure GM1 Foundation by Christine Waggoner, Founder & President of the Cure GM1 Foundation, and by Chrystal Palaty, medical writer.

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

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

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Point of Contact: Please contact Christine Waggoner, Founder & President, Cure GM1 Foundation, info@curegm1.org, for questions related to this report.

Acknowledgements

Cure GM1 Foundation is incredibly grateful for opportunity to share our experiences with the FDA and the entire GM1 gangliosidosis community through our externally led patient-focused drug development (EL-PFDD) meeting. Our hope is that this meeting results in treatments for everyone living with GM1 gangliosidosis.

Thank you to all those from the U.S. Food and Drug Administration who took the time to attend this meeting and for reading this report. We wish to thank Shannon Sparklin and Karen Jackler from the FDA who guided us through this process.

Thank you to Dr. Wilson Bryan from the FDA for your perspectives on the importance of El-PFDD meetings, to Dr. Tifft for the very interesting clinical overview of GM1, and to Dr. Jarnes for outlining the treatment landscape.

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Thank you to all the representatives from advocacy groups, biotech companies, federal agencies, and research groups throughout the world who attended this meeting.

We extend our deepest thanks to all of the individuals living with GM1 and their parents and caregivers who shared their experiences and insights at the meeting. Thank you to our discussion starters, Zoom panelists, and to all of you who called or wrote in. We hope that this meeting accurately reflects your voice and insights.

Executive Summary

Cure GM1 Foundation hosted the GM1 Gangliosidosis Externally-Led Patient Focused Drug Development (EL-PFDD) meeting on October 14, 2022. This meeting was held to provide a patient and caregiver perspective of the symptoms and burdens associated with GM1 gangliosidosis (GM1) in daily life, as well as the massive unmet treatment needs experienced by patients and families who live with GM1 every day. The meeting was held virtually to enable as many community members to participate as possible and to allow many different voices to be heard.

This EL-PFDD meeting was modeled after the work of the FDA's Patient Focused Drug Development (PFDD) initiative. PFDD is a systematic way of gathering patient perspectives on their condition and on available treatments. The information gathered at the meeting is presented in this *Voice of the Patient* report, a high-level summary of the perspectives generously shared by the families and caregivers of individuals living with GM1 gangliosidosis, who participated in the October 14, 2022, EL-PFDD meeting. The report also includes selected comments that were submitted through an online portal.

The information in the *Voice of the Patient* report may be used to guide therapeutic development and inform the FDA's benefit-risk evaluations when assessing therapies to address GM1. The hope is that this information will catalyze better treatments and ultimately a cure for all those affected by GM1.

Cure GM1 Foundation has provided this report to the FDA, government agencies, regulatory authorities, medical product developers, academics, and clinicians, and it is publicly available for the many stakeholders in the GM1 community. The input received from the October 14, 2022, EL-PFDD meeting reflects a wide range of GM1 experiences, however not all symptoms and impacts may be captured in this report.

Key Points about GM1 Gangliosidosis

1. **GM1 gangliosidosis is a neurodegenerative disease which progressively destroys nerve cells in the brain and the spinal cord**. After a period of normal development, children and adolescents living with GM1 heartbreakingly regress and start to lose all their abilities.
2. **GM1 has a relentless progression from onset, which eventually results in premature death**.
3. **GM1 has an exceptionally high patient burden and all individuals living with GM1 are profoundly affected.** All individuals living with GM1 experience regression, pain, impaired mobility, communication issues and cognitive impairment, in addition to experiencing many other disease-related health concerns.
4. **Individuals living with GM1 are entirely dependent on their caregivers for almost everything.** They become unable to move and their communication is greatly impaired. Most are unable to communicate their pain, their needs, and their preferences.
5. **Parents experience so many worries for their loved ones, especially about their diminishing quality of life.** In addition, parents worry about uncontrolled pain, premature death, worsening symptoms, and uncontrolled seizures.

6. **Treatments for people living with GM1 are urgently and desperately needed.** There are no FDA-approved disease-modifying treatments for GM1.
7. **Medications are available to help manage GM1 symptoms, but they don't halt disease progression.** These include medications for pain, sleep, and seizure management.
8. **Individuals living with GM1 require intensive physical and occupational therapy and extensive amounts of equipment for support**. Supports are also often needed for breathing and feeding. Current GM1 treatment approaches only treat some, not all of the symptoms, are not very effective, and availability/accessibility is limited. Most importantly, the disease still progresses.
9. **Many have invested hope in experimental therapies including gene therapy**. Experimental therapies are not accessible to all, they often depend on early diagnosis, are accompanied by great risk and outcomes are variable.
10. **Short of a complete cure, parents would like a slowing or stopping of disease progression.** Parents emphasised that almost any improvement to quality of life would be welcome.

Contents

Clinical Overview and Meeting Summary

GM1 Gangliosidosis Clinical Overview, Research and Treatment Landscapes[1]

GM1 gangliosidosis is a rare neurodegenerative disease caused by variants in the *GLB1* gene. *GLB1* encodes an enzyme called ß-galactosidase which breaks down GM1 gangliosides. Each of the different *GLB1* gene variants causes a deficiency or functional impairment in the ß-galactosidase enzyme. The result is that GM1 gangliosides accumulate in the lysosome, eventually leading to cell death. When neurons die they are not replaced, leading to neurodegenerative symptoms, however, all systems in the body are affected. Disease severity is related to the amount of residual ß-galactosidase in the cell.

GM1 gangliosidosis is classified as a lysosomal storage disorder. While lysosomal storage disorders are collectively uncommon (1 in 5000 births), GM1 gangliosidosis is extremely rare, occurring 1 in 100,000-200,000 births. GM1 gangliosidosis is an autosomal recessive disorder, so both parents must carry a copy of the mutated gene. While GM1 occurs globally, there is an increased prevalence in Malta, Brazil, and among the Romani people, due to founder mutations.

GM1 gangliosidosis exists as a disease continuum, with variability in both the age of onset and rate of disease progression. Pediatric GM1 gangliosidosis is divided into three types based on age at symptom onset[2], in addition to adult-onset disease.

1. **Early infantile GM1 (Type 1):** Onset of symptoms at under 12 months of age
2. **Late infantile GM1 (Type 2A)**: Onset of symptoms at 1 to 3 years of age
3. **Juvenile GM1 (Type 2B)**: Onset of symptoms at 3 to 10 years of age
4. **Adult onset GM1 (Type 3)**

Symptom presence and severity and rate of decline vary across and within the three pediatric subtypes. Type 1 features include cherry red spots; coarse facial features; developmental delays and cognitive impairment; central nervous system dysfunction, including hypotonia and heightened startle reflex; and skeletal dysplasia.

In children with types 2A and 2B, features include clumsiness and progressive motor abnormalities, corneal clouding, and regression of cognitive skills and other developmental milestones. Other features reported across subtypes include seizures; gastrointestinal symptoms, such as constipation; impaired muscle tone and mobility; choking; and aspiration.

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[1] This is a summary of presentations provided by Dr. Cynthia Tifft, Deputy Clinical Director, National Human Genome Research Institute and Dr. Jeanine Jarnes, Assistant Professor, Department of Pediatrics at the University of Minnesota Medical School, at the GM1 Gangliosidase EL-PFDD meeting on October 14, 2022.

[2] Descriptions of the three pediatric forms of GM1 were adapted from: Bingaman A, Waggoner C, Andrews SM, et al: *GM1-gangliosidosis: The caregivers' assessments of symptom impact and most important symptoms to treat.* American Journal of Medical Genetics Part A 191:408-423, 2023. The abstract is included in **Appendix 7** of this report.

The expected lifespan of children with type 1 is 2 to 3 years of age. For children with type 2A the expected lifespan is 5 to 10 years of age, and for type 2B is young to middle adulthood.

Adult onset GM1 (Type 3) is characterized by gait disturbance, dystonia, impaired speech, and decreased cognition. While this is very rare, there is an increased incidence in Japan. The lifespan is variable.

An early diagnosis is essential for successful treatment. Many therapeutic approaches for GM1 are being investigated including small molecules and pharmacologic chaperones, enzyme replacement therapies, and gene therapies.

Meeting summary

The GM1 Gangliosidosis Externally-Led Patient Focused Drug Development (EL-PFDD) meeting was held virtually on October 14, 2022. This meeting represented an important opportunity for caregivers to share their experiences and perspectives with FDA staff and other key stakeholders about the challenges and unmet treatment needs of those living with GM1 gangliosidosis (GM1). The GM1 Gangliosidosis EL-PFDD meeting was co-moderated by Christine Waggoner, Founder & President, Cure GM1 Foundation, and by James Valentine, JD, MHS, from Hyman, Phelps and McNamara.

Christine Waggoner opened the meeting by introducing the mission of the Cure GM1 Foundation and providing a brief introduction to GM1 gangliosidosis. She asked meeting attendees, including members of the FDA, to listen carefully to the stories from the GM1 community and to imagine what the lives of patients and families are like. **Dr. Wilson Bryan**, the Director of the Office of Tissues and Advanced Therapies and the Center for Biologics Evaluation and Research (CBER) at the FDA provided opening comments from the FDA perspective. He shared that information learned at this PFDD meeting will be valuable to help the FDA to think about how clinical trials should be designed, what endpoints are most meaningful to patients, and how to best balance benefits and risks of new treatments. **Dr. Cynthia Tifft**, Deputy Clinical Director, National Human Genome Research Institute, presented a clinical overview of GM1 to create a scientific foundation for the rest of the meeting. Key points from her presentation are summarized in the clinical overview on the previous page.

Christine Waggoner introduced her co-moderator, **James Valentine**, JD, MHS who provided an overview of the meeting structure and encouraged the parents, caregivers and family members of those living with GM1 to contribute to the dialogue via online polling, calling in by phone, and contributing written comments using the online portal.

Individuals with GM1 are unable to communicate so were represented by their parents and caregivers during the meeting.

Online polling was used to determine the demographics of the individuals living with GM1 who were represented by meeting attendees and the results are presented in **Appendix 1.** The full spectrum of GM1 gangliosidosis was represented at the meeting, with more than half of the meeting participants representing patients with Type 2A, late infantile, and about one fifth of meeting participants each representing patients with Type 2B, juvenile and Type 1, infantile GM1. A small percentage of attendees represented those living with Type 3, adult onset GM1.

Attendees were situated across the US, with almost half from the Eastern time zone, as well as in Canada. There were slightly more female patients represented than males. There was a strong representation from across the different pediatric age ranges, with most patients being between the ages of 1 – 20 years, reflecting that GM1 is primarily a pediatric disease. All individuals with GM1 represented at the meeting were diagnosed by the age of 10 years, with 13 - 36 months (1-3 years) as the most common age range of diagnosis.

The GM1 EL-PFDD meeting was structured around two key topics. Session 1 was *Living with GM1 Gangliosidosis*. Session 2 was *Current and Future Treatments for GM1*. The meeting agenda is in **Appendix 2**, and questions provided for meeting discussion are in **Appendix 3**.

The morning session continued with a pre-recorded panel of parents and caregivers who were selected to represent a range of GM1 gangliosidosis disease types and experiences. James Valentine moderated a discussion between several caregivers who served on a live Zoom panel as well as those who dialed in by phone. Additional relevant comments entered through an online submission form were read by Christine Waggoner. The names of panelists and callers are listed in **Appendix 4.**

The afternoon session opened with a presentation by **Dr. Jeanine Jarnes**, Assistant Professor in the Department of Pediatrics at the University of Minnesota Medical School. She discussed some of the challenges and opportunities for therapies and then did a deep dive into potential therapies currently in development. Her presentation was followed by a pre-recorded panel of parents and caregivers who described different medical therapies and other approaches they used. Again, meeting attendees participated in online polling, called in and submitted written comments which were added to the moderated discussion by James Valentine and Christine Waggoner. At the end of the meeting, **Larry Bauer**, RN, MA provided a reflective summary of the key meeting messages and Christine Waggoneer concluded the meeting by thanking all the participants and attendees.

The online polling results from Topics 1 and 2 are included in **Appendices 5** and **6**, respectively. **Appendix 7** contains the abstract of a recent Caregiver Study[3], which was conducted to identify parents' and caregivers' preferences of the most important pediatric GM1 symptoms to treat. Caregiver Study results are described throughout this report and shaded in grey. To include as many voices as possible, the online comment submission portal was open for four weeks after the meeting. All submitted comments are included in **Appendix 8**, with selected comments included in the body of this report.

This *Voice of the Patient* report is provided to all GM1 community members and stakeholders including the US FDA, other government agencies, regulatory authorities, medical product developers, academics, clinicians, and any other interested individuals. The final report, and a video of the meeting can be found at https://curegm1.org/pfdd/. According to YouTube statistics, the meeting has been streamed over 700 times as of February 15, 2023.

[3] Bingaman A, Waggoner C, Andrews SM, et al: *GM1-gangliosidosis: The caregivers' assessments of symptom impact and most important symptoms to treat.* American Journal of Medical Genetics Part A 191:408-423, 2023.

Session 1: Living with GM1 Gangliosidosis

During the EL-PFDD meeting, parents and caregivers shared their perspectives and experiences of living with GM1 gangliosidosis. Parents and caregivers described the emergence of the first, disturbing symptoms in their children, followed by long diagnostic journeys and then the bewilderment and grief of a GM1 gangliosidosis diagnosis. Many parents described how their children were "late bloomers" who were unable to meet developmental milestones, before they began to regress. Parents and caregivers used online polling to select all the GM1-related health concerns that their loved ones experienced. They chose the top three most troublesome, they described the impacts that GM1 had on activities of daily living, and shared their worries for the future.

This section is organized by the results of the online polls and illustrated with parent and caregiver quotes both from the meeting and from those submitted online. Important points that were emphasized during the meeting but were not captured by the polls are indicated as such.

Q1 & Q2: GM1 gangliosidosis has an extremely high patient burden

Meeting attendees used online polling to first select all the GM1-related health concerns that they, or their loved ones, had ever experienced. They then selected their three most troublesome. Poll results are in **Appendix 5, Q1 and Q2** and described below**.**

All individuals with GM1 experience an extraordinarily high number of disease-related health concerns, with parents and caregivers each selecting an average of 9.7 disease-related symptoms. According to the poll results, impaired mobility was the most troublesome, followed by communication issues, cognitive impairment, and seizures. Notably, the poll responses did not include regression and pain, which are two characteristics that were mentioned more frequently than any of the other health concerns.

Regression

Regression is an important aspect of GM1, described by all parents and caregivers. Regression impacts all other symptoms. Some described how their children initially developed normally, then gradually began to lose all their acquired skills.

> "*[Our daughter's]* ***development plateaued*** *at the age of one, and then she* ***started to regress****. At first, we noticed that she did not move her hands and legs that much. She was not following the pictures we showed her as she did before. Also, she had more problems with feeding.* ***It was a really slow regression and we realized that this is not going to stop***." - Bence, father of a two-year-old girl living with Type 1, infantile GM1

> *"She could pick things up and read through a book on her own, look through a book. But gradually, those skills started to regress. And then really out of the blue, … I can distinctly remember just over a course of a couple days, she wouldn't walk anymore, she would just stand there. …* ***I can barely ever go back and look at pictures or videos from a couple years ago,*** *just because I can see what [our daughter] used to be able to do and now that she can't. There's just a* ***profound sadness*** *to look at those things and remember* ***an innocent life, a time before we knew what her diagnosis was****."* - Matt, father of a five-year-old daughter living with Type 2A, late infantile GM1

"*One of the most frustrating aspects of juvenile GM1 is that it **doesn't just limit their future, but it robs them of their past abilities as well**. Explaining to a child why they're not able to do things that they were once able to do is heartbreakingly impossible, comforting them even though they can't tell you that they're upset because their friends can do things that they cannot*." - Kylie, mother of nine and six-year-old daughters living with Type 2B, juvenile GM1

*"**She is aware of how GM1 is taking over her body and she can do fewer and fewer things**, she still walks but **it is agony to think how much time is left**, how much time is left to listen to that thread of voice, or how much time is left to use your hands*." - María José, mother of a 20-year-old daughter living with Type 3, adult onset GM1

The Caregiver Study noted that regression of previously acquired skills was associated with distress for both parents and children.

Pain

Pain was one of the most frequently mentioned GM1-related health concerns. Pain seems to increase as the disease progresses, often becoming severe and uncontrollable.

*"She **struggled to sleep** and would **wake up screaming in pain** multiple times daily."* - Tania, grandmother of a granddaughter with Type 1, infantile GM1 who passed away

*"Recently, [our daughter] has been having **severe pain that lasts for 12 hours**. She loses her voice from the **intensity of screaming**. She **twists, turns, and stiffens** as the **pain consumes her entire body**. Nothing will console her. All we can do is watch her cry out with **no rescue in sight**. In these moments, it feels like the **pain will never end***." - Megan, mother of a five-year-old daughter living with Type 2A, late infantile GM1

*"**She's in pain or discomfort almost the whole day**. I spend quite a long time trying to help her find TV that interests her since distraction is one of the main forms of pain management."* Douglas also described how seizure medication damaged his daughter's teeth, "*For eight months, **she was in constant pain because the teeth left shards in her gum**, but the hospital COVID-19 restrictions kept her from getting the surgery she needed.* - Douglas, father of a 14-year-old girl living with Type 2B, juvenile GM1

Karen, mother of a daughter living with Type 3, adult-onset GM1, said that her daughter experienced, "*A complete loss of mobility and **24/7 pain***".

Pain was also an important symptom identified in the Caregiver Study, where it was described as both a challenging symptom to treat and a source of worry, as parents and caregivers feared that the child was experiencing pain that they were unable communicate to them.

Impaired mobility or loss of mobility

Every individual living with GM1 experiences impaired mobility and this is often one of the first symptoms of GM1. Impaired mobility was also selected as the most troublesome symptom. Falls become increasingly common as the disease progresses, and in later stages of disease, patients can no longer even move to make themselves comfortable.

*"Watching her go from pushing herself up and developing normally and then **regressing and losing the ability** to do something as simple as push herself up during tummy time was heartbreaking."* - Tania, grandmother of a granddaughter with Type 1, infantile GM1 who passed away

*"Early on in her life, she was able to walk a bit on her own. She could move around and cruise around the house, around furniture. …**Over the course of a few days, she just stopped walking abruptly**."* - Matt, father of a five-year-old daughter living with Type 2A, late infantile GM1

Ryan noticed his daughter's foot, *"Slightly turning inward as she walked. …At three, we noticed that she was **falling more regularly**",* and she walked on her tip toes. - Ryan, parent of an eight-year-old daughter living with Type 2B, juvenile GM1

"*Now [our daughter] is 14. She can **no longer walk, talk, eat, scratch and itch, or make herself comfortable** in any kind of meaningful way. When she moves, **she can only rotate her head backwards**, her head gets stuck backward constantly in a way that limits her airways."* - Douglas, father of a 14-year-old girl living with Type 2B, juvenile GM1

Communication issues

All individuals living with GM1 have difficulties communicating. Most are unable to speak clearly, some are unable to control the volume of their vocalizations. Parents and caregivers selected this as the second most troublesome symptom after mobility issues.

"*It wasn't until age seven that she started to sit and move differently on the floor. She fell a lot. We thought it could be some sort of inner ear problem. At age eight, **she began to stutter and speak badly**."* - São, mother of a 14-year-old daughter living with Type 2B, juvenile GM1

*"Both of our girls are very **difficult to understand** verbally, especially when the context of their discussion is unknown. They love to come home from school to tell us about their day, but oftentimes we're **unable to understand what they're trying to tell us**. Simple things like telling us their stomach hurts or they have a headache is nearly **impossible for them to communicate**."* - Kylie, mother of nine and six-year-old daughters living with Type 2B, juvenile GM1

*"Our son still talks. **He doesn't talk in the same way that he did when he was younger**; he talked completely typical normal when he was small. But as he lost the ability to talk, he also **lost the ability to control the volume** that he talks at. When he does speak, it's **very loud** and it can be sort of **disruptive**."* - Cindy, mother of a 34-year-old son living with an unusual form of GM1 with both juvenile and adult-onset characteristics

Cognitive impairment/intellectual disabilities

All individuals living with GM1 experience cognitive impairment and intellectual disabilities. Just over a third of parents/caregivers selected this as one of their top three most troublesome health concerns.

*"[My son] is **developmentally delayed**, so **he doesn't pick up new skills**, which makes it **difficult for him to gain new abilities** in order to eventually be self-sufficient."* - Abby, mother of a son living with Type 1, infantile GM1

"*Around 18 months, family and friends began to comment on how [our daughter] was a **late bloomer, taking her time walking and talking***." - Megan, mother of a five-year-old daughter living with Type 2A, late infantile GM1

*"We first started noticing delays with [our daughter's] development when she was around three years old. We could tell she had **speech delays** and she was also **very clumsy**, especially for a kid whose parents were extremely athletic. By age four, we knew something was definitely wrong. She wasn't just having delays. It was like **one day she could do things and the next day she couldn't**."* - Kylie, mother of nine and six-year-old daughters living with Type 2B, juvenile GM1

Seizures

Half of individuals living with GM1 experience seizures, and this was selected as one of the most troublesome GM1-related health concerns by almost a third of parents and caregivers. Some described how their children experience hundreds of seizures a day and will sometimes stop breathing during a seizure. Others noted that pain can exacerbate seizure activity.

*"The **seizures have been the most difficult part of the journey**. Our whole lives revolve around them. We can't go to certain places in fear he will get too excited or stimulated and have a seizure. … Every time he has a seizure I think, is this it? **Will this be his last breath?**"* - Rojan, mother of a five-year-old son living with Type 2A, late infantile GM1

Other GM1-related symptoms mentioned in the polls

These include breathing difficulties, muscle weakness (hypotonia), muscle stiffness (dystonia, spasticity), bowel or bladder issues (constipation, difficulty urinating), scoliosis and/or hip issues, impaired fine motor skills, anxiety or psychological problems, and visual issues.

Breathing difficulties, including aspiration and choking, were a concern especially for parents of children with Type 1 infantile GM1.

"*During the course of time he had problems with **breathing normally** and **swallowing**."* - Manuel, father of a child with Type 1 infantile GM1 who passed away

*"Since he has been **regressing** lately, he is having **issues with [oxygen] desaturations**, thus it has restricted him to being **dependent on a high flow machine 24/7**."* - Ronnie, father of a 10-month-old infant son living with Type 1, infantile GM1

Muscle weakness (hypotonia) contributes to many of the GM1-related health impacts including sleep, reflux, oral and respiratory secretions, head control and the inability to sit up.

*"Having **low muscle tone**, he **cannot sit, roll over, or crawl on his own**, so his life most of the time consists of laying down, being held, or sitting with support."* - Abby, mother of a son living with Type 1, infantile GM1

*"I think that the most difficult symptom has been the **hypotonia**, because it really **underpins a lot of the other issues** that we have with him, including sleep difficulties. It*

*causes him to have **obstructive sleep apnea**, so he wakes up all the time. He's never gotten good restful sleep."* – Stephanie, mother of a one-and-a-half-year-old son living with Type 2A, late infantile GM1

Sleep difficulties including sleep apnea can affect the entire family. Reflux and pain only make sleep difficulties worse.

Poor sleep affects all of her son's other symptoms including pain and regression. "*I notice **the pain is worse**. Obviously, you need your sleep to be able to help repair your body. So, **if he's not sleeping well, I notice he's in a lot more pain**, and that's really difficult. And then also, I noticed that he will **lose skills more quickly** when he's not sleeping well as well."* - Stephanie, mother of a one-and-a-half-year-old son living with Type 2A, late infantile GM1

Muscle stiffness (dystonia, spasticity) can have severe consequences, damaging teeth and the inside of the mouth.

"*She was a massive **teeth grinder from the dystonia**. During that time, she **bit down on her** tongue for 10 minutes before I could get her to loosen her jaw long enough to get her tongue out*." - Douglas, father of a 14-year-old daughter living with Type 2B, juvenile GM1

Scoliosis or hip issues as a result of GM1-related skeletal changes are painful and require surgery.

*"The **avascular necrosis** in his hips cause him **great pain during transitions**, and he is currently being evaluated for a **hip replacement**."* - Debra, parent of a 19-year-old son living with Type 2B, juvenile GM1

Impaired fine motor skills. When these are lost, children can't play with their toys or enjoy activities that others take for granted.

*"The **toys that she could once play with, she couldn't touch them anymore** when she lost the ability to move her hands and her legs."* - Tania, grandmother of a granddaughter with Type 1, infantile GM1 who passed away

"*He used to be able to play with toys, which was helpful, but **he's lost the ability**, his fine motor skills. **He can't pull a toy, hold a rattle, do anything like that**."* - Brittany, mother of a two-and-a-half-year-old son living with Type 2A, late infantile GM1

*"She **cannot write, read, or hold her pencil**. She **cannot even put her jacket and shoes on independently**."* - Kylie, mother of nine and six-year-old daughters living with Type 2B, juvenile GM1

GM1-related symptoms not captured in the polls

Oral and respiratory secretions. Many parents described how this can be so extreme that it results in choking and can require suctioning.

*"It happens just automatically, there's no warning. It's just all of a sudden, she's **gagging on her saliva and she's not able to clear it**. So, we have to go over and sit her up and*

pat her on the back." This happens both night and day. *"We've gradually gotten to the point where we are seeing her do this **at least six to eight times a day**."* - Jenny, mother of an eight-and-a-half-year-old daughter living with Type 2A, late infantile GM1

Swelling/edema and loss of eyesight

"*Of all the symptoms, the most significant to my son was the swelling. By the end, **he was so swollen he could barely move** and he **couldn't even smile anymore**. He couldn't walk. He lost his ability to sit up and then he **lost his eyesight** along with being able to move his arms and smile, so he wasn't able to play anymore or even watch TV*." - Nolan, parent of a child with Type 1 infantile GM1 who passed away

Frequent illnesses

"*At the age of 15 months, she **caught an infection** and we needed to go to the hospital with her, and this is when the GM1 really started to show itself. She was very ill. She was **intubated for weeks**. She beat three pneumonias."*- Bence, father of a two-year-old girl living with Type 1, infantile GM1

Because of her daughter's high susceptibility to illness*, "It was very **hard to participate in everyday activities such as school, social gatherings, and travel**."*- Katie, mother of a child living with GM1

The symptoms identified during the EL-PFDD meeting are consistent with those identified during the Caregiver Study but were prioritized differently. A difference was that the Caregiver Study only included caregivers of pediatric GM1 patients and separated responses by GM1 disease type. Respondents in the Caregiver Study also felt that some types of GM1 symptoms were closely interrelated and could not be separated when determining relative importance, which may have influenced their selection.

Q3: GM1 patients are entirely dependent on their caregivers for almost everything. They are unable to move and their communication is greatly impaired. All activities of daily life are impacted

Meeting attendees again used online polling to select the top three activities of daily life that are important for their loved ones that they are unable to do or struggle with because of GM1. Poll results are in **Appendix 5, Q3** and are described below with patient quotes.

GM1 is characterized by a high caregiver burden. Patients are completely dependent on their parents for all activities of daily living, and many require 24-hour care.

This was not captured in the polls but was described throughout the meeting.

"*She needs **24-hour care every single day of the week**. It is not easy, but **we love her so much**. She could make us the happiest person in the world with a single smile."* - Bence, father of a two-year-old girl living with Type 1, infantile GM1

*"He has **regressed really truly to about a three-month-old**, so it's very difficult. He's definitely **100% dependent upon me**. I just don't feel this is a life for a nearly 14-year-old."* - Lindy, mother of a 14-year-old son living with Type 2A, late infantile GM1

Tom's daughter requires, "***One-on-one support … throughout the day****. This includes food preparation, feeding, social activities, hygiene, and dress*." - Tom, father of an 18-year-old daughter living with Type 2B, juvenile GM1

"We ***feed her, change her diapers, give her showers and do everything*** *for her*." - Ruth, mother of a 20-year-old daughter living with Type 2B, juvenile GM1

This theme was reflected in the results of the Caregiver Study which acknowledged the high caregiver and patient burden of GM1.

Communicating needs or wants is impossible

Communicating needs or wants was the top activity of daily life that individuals living with GM1 struggle with, as selected by parents and caregivers in the online poll. Individuals living with GM1 are unable to ask for what they need. Although many are non-verbal, some communicate their love and affection with eye contact, smiles and even squeals of delight, however these interactions diminish with time and as pain progresses.

"She is stuck waiting, ***waiting for someone to pick her up, waiting for help, waiting****. In the waiting,* ***she cannot communicate her needs, her wants, or her dreams****. We can only guess. She attempts to use an eye gaze system and communication buttons to give her a voice, but the reality is,* ***we will never hear our child's beautiful voic****e, so we must speak for her."* - Megan, mother of a five-year-old daughter living with Type 2A, late infantile GM1

"***I've never ever heard my son say, 'Mommy, I love you.'*** *That is incredibly difficult. Just overall communication. Just being able to let me know if he needs something or is in pain or scared or sad or excited or happy*." - Lindy, mother of a 14-year-old son living with Type 2A, late infantile GM1'

Most distressingly for parents, most living with GM1 are unable to indicate when they are experiencing pain.

"My daughter's ***not able to tell me when she's in pain, when she is hurting****. I just have to guess. … I can just see her face. Just guessing what's going on in her body.*" – Ruth, mother of 20-year-old daughter living with Type 2B, juvenile GM1

"*The worst thing is* ***she cannot talk about the pain and show where it hurts***." - Victoria, mother of an adult daughter living with GM1

Impaired communication was selected as the most impactful GM1 symptom in the Caregiver Study. Parents of children with Type 1 identified communication and awareness of, and engagement with, caregivers as their top two symptoms. Parents of children with Types 2A and 2B, selected communication as their most impactful symptom, particularly expressive communication.

Getting around and mobility impacts, limit other activities like social engagements and travel

Parents and caregivers selected getting around and mobility as one of the biggest impacts of GM1. Stairs can limit visits to family and friends in their homes. Getting out is hard when patients require so much equipment including oxygen tanks, special food and incontinence

supplies, and some are fearful of leaving home. Accessibility is not only about how to accommodate wheelchairs, but also about having appropriate places to change diapers.

Challenges with getting around and mobility impact many of the other activities selected in the polls, including participation in social engagements/events/sports as well as travel and vacationing. These activities are all grouped here together.

> *"Every time we go to visit family, we need to pack not only the normal baby items, but also **pre-made bottles**, and **make sure he has enough oxygen** to last while we are gone*. - Abby, mother of a son living with Type 1, infantile GM1
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> *"The loss of mobility affected [our daughter], both physically and mentally. Playing with her sister and friends now looked different, and exploring her world became a lot smaller. **She's sad, confused, and frustrated as to why she cannot do what she used to**."* - Megan, mother of a five-year-old daughter living with Type 2A, late infantile GM1
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> *"When we go to new playgrounds, **they want so badly to be able to climb and play like normal kids**, but are not able to*." - Kylie, mother of nine and six-year-old daughters living with Type 2B, juvenile GM1
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> *"[Our son] has the mental capacity of a 1 to 2-year-old. He is **incontinent and requires a wheelchair**. We've found travel by plane too difficult …but have continued to travel with him by RV. …We **can't do everything we want to do together**, but there are quite a few activities we can do, and he really seems to enjoy traveling."* - Debra, parent of a 19-year-old son living with Type 2B, juvenile GM1
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> Cindy's son's loud vocalizations make travel on an airplane and being in public spaces difficult. She described how he can't attend his sister's basketball games because his wheelchair can't access the stands and being positioned on the sidelines is too intense. *"Accessibility issues are better in our world than they used to be, but they're not perfect. …He's 34. He's the size of an adult, so you **can't pick him up and carry him** somewhere. …We ended up having to figure out a way to attend her games individually, so **we never got to go as a family**."* - Cindy, mother of a 34-year-old son living with an unusual form of GM1 with both juvenile and adult-onset characteristics

Socializing with peers/siblings becomes harder and harder as abilities decline

Socializing with peers and siblings is another activity significantly impacted by GM1, and challenges with communication, mobility, and cognition all play a role. Parents and children find it distressing to see how much they are falling behind their peers. Some experience rejection and stigma.

> *"[Our niece] clearly enjoys interacting with people most of all, but **she cannot ask for attention or interact with her sibling, peers, and family** without the other individual taking the initiative to interact with her. The older she gets, the less likely people outside of her immediate family and caregivers are to take that initiative. **Peer interactions are certainly missing from her life most days**. Even her interactions with her brother and cousins are often cut short because **they can run and play and she cannot follow***." - Honey, aunt of a niece living with Type 2A, late infantile GM1

*"Just typical two-and-a-half-year-old things - **going on play dates with friends -those pretty much don't happen for us** because I'm worried. He is wheelchair bound. **He can't sit up or crawl or walk**. I'm wondering if the house we're going to has room for his wheelchair, if the park we're going to has a comfortable place for him to lay, if the kids are going to talk to him because **he kind of just lays there. He can't really interact with anybody**. So that's really hard*." - Brittany, mother of a two-and-a-half-year-old son living with Type 2A, late infantile GM1

*"The simplest things that used to make us extremely happy, like **hanging out with our friends and family, oftentimes can be emotionally difficult** now. Seeing kids who are typical can really make you realize how far gone your child is, although you're still so happy that they're here with you."* - Kylie, mother of nine and six-year-old daughters living with Type 2B, juvenile GM1

*"She cannot keep up with others, especially with young people her age. She **suffers from the loneliness of friends and that leads her to suffer from depression**. …She **isolates herself** more and more, she feels that she **never fits in** anywhere. I see how the ones around her advance and **she is stuck**."* - María José, mother of a 20-year-old daughter living with Type 3, adult onset GM1

Self-care, including bathing and dressing, is significantly impacted by GM1 as children rely on their parents for everything

*"My grandchild can't walk, talk, hold up her head, sit on her own, eat (she's on a feeding tube), move her bowels without external assistance, interact with those around her, and her symptoms increase and worsen at an alarming rate. **Time is the enemy with GM1**. **It deprives its victims of abilities to function in every way**."* - Melinda, grandmother of a granddaughter living with Type 2A, late infantile GM1

*"[As our daughter's caregiver] **I spend at least 15 to 60 minutes of every hour helping her**. I feed her 12 to 13 times a day change 10 to 14 diapers a day. Being very hydrated helps her dry eyes, give her medicine six to 10 times a day. I give her about 70 to 80 minutes of physical therapy every day. She gets an enema every day so she can poop and I hold her on the toilet for about 10 minutes. **I sleep next to her bed on the floor every night to help her with seizures, nightmares, and her difficulty sleeping**."* - Douglas, father of a 14-year-old girl living with Type 2B, juvenile GM1

Ability to eat by mouth becomes harder and many children require a tube

"*His eating is the most significant symptom because **some days he can eat a good amount, and other days he struggles to eat**. This is **very stressful for us as parents** because we don't want to see him struggle with nutrition and **we worry about him needing to be on a feeding tube** at any point*." - Abby, mother of a son living with Type 1, infantile GM1

*"He has **significant feeding issues** because he just doesn't have the **tone in his mouth muscles** and his **ability to swallow**, and so we are constantly **afraid of him choking on his food**."* - Stephanie, mother of a one-and-a-half-year-old son living with Type 2A late infantile GM1

> *"It's also harder and **harder for her to chew**. …Even to feed her now, I can see that **she's having trouble moving her tongue from side to side** or being able to chew the food. I have to cut it so small and find foods that she's able to actually swallow, with the **fear of one day, she will have to have a G-tube**."* - Ruth, mother of a 20-year-old daughter living with Type 2B, juvenile GM1

Attending school or having a job

Children living with GM1 have many challenges attending school and none of them will have the opportunity to find employment.

> *"She can no **longer go to school without me** after the school became overwhelmed with her having **cluster seizures and throwing up every day**. I spend two or more hours a day taking her to school."* - Douglas, father of a 14-year-old girl living with Type 2B, juvenile GM1

> *"She attends a regular school but with **special education**. She has **many difficulties**, but we try to encourage and help her so that she doesn't lose her abilities."* - São, mother of a 14-year-old daughter living with Type 2B, juvenile GM1

As care for an individual with GM1 is a 24/7 proposition, many parents and caregivers no longer work outside the home. Many parents have a hard time finding other caregivers to help.

> "*As a mother, I feel like **I am not able to work outside of the home** and give him the life that he needs. He has **complex needs that I feel would not be met in a daycare**. …I have only left [my son] once or twice with my mother while I ran errands. **I don't feel comfortable leaving him** and it also bums me out because most parents can drop their kids off to their grandparents for a sleepover and I'm not able to do that."* - Abby, mother of a son living with Type 1, infantile GM1

> *"[Because of his seizures] caregivers and family are nervous to care for him without one of us present. Therefore, **my husband and I have not gone anywhere overnight since his diagnosis**."* - Rojan, mother of a five-year-old son living with Type 2A, late infantile GM1

Q4: Parents and caregivers experience many worries for their loved ones, especially about their diminishing quality of life

Parents and caregivers used online polling to select their top three worries about their loved one's condition in the future, but some found it difficult to limit their selection to just three.

> *"I just want to start off by saying sometimes picking these top three, I find it incredibly difficult as a parent because all of them are a huge concern for us. …When you get a terminal, progressive disease diagnosis, all you think about is the future, what your child is doing now, what they're not going to be able to do, and how much time you have left with them. **Not a Christmas goes by where I don't wonder how many more Christmases we'll have with my daughter**."* - Jenny, mother of an eight-and-a-half-year-old daughter living with Type 2A, late infantile GM1

In addition to worrying about uncontrolled pain, premature death, worsening symptoms and uncontrolled seizures, parents worried about their children's diminishing quality of life, which

seemed to include all other worries. Poll results are shown in **Appendix A, Q4** and listed in descending order below with patient quotes.

Declining quality of life was a worry mentioned throughout the meeting.

This was not included as a poll response, but throughout the meeting many parents expressed very similar worries about their loved ones' declining quality of life. Some worried that their loved ones' suffering would increase to the point that they had no quality of life at all.

> ***"I worry about the future*** *if there's a time when I won't be able to interact with her on any level. … I worry about pain increasing and not being able to be controlled as everyone does. I worry about seizures. They haven't happened yet to my knowledge, but I hear people talk about them and it haunts me. I worry that she won't be able to hear, that she won't be able to see again*. … ***I worry about the quality of her life degrading to where she has no pleasure at all in being alive."*** - Melinda, grandmother of a granddaughter living with Type 2A, late infantile GM1

> "*The future is an extremely scary prospect. We know they could live to be in their teens, 20's, or perhaps even 30's. We don't know, however,* ***what their quality of life will be*** *at any point. Will they be able to walk? Will they be able to talk? Will they even know who we are? And honestly,* ***the scariest thing for us as parents is whether or not we will know when they've regressed to the point where medical intervention perhaps isn't in the best interest****.* - Kylie, mother of nine and six-year-old daughters living with Type 2B, juvenile GM1

Uncontrolled pain was the top worry selected in the polls

> *"Our greatest fear is that she will have* ***more pain as the disease progresses****, and* ***we will lose her too soon****, but at the moment, she's stable and that is all that matters*."- Bence, father of a two-year-old girl living with Type 1, infantile GM1

> "***Uncontrolled pain****… is something I continue to worry about for my daughter.* ***She grinds her teeth and is clearly in pain*** *with her arms tight. And we continue to try to manage it, but it's very hard because not being able to communicate,* ***it's hard to tell if it's frustration or pain or an irritatio****n or what it is that's going on with her."* - Jenny, mother of an eight-and-a-half-year-old daughter living with Type 2A, late infantile GM1

> "*For the pain and the seizure activity …to increase exponentially to a point that my poor son is just in a* ***constant state of seizure*** *or* ***trying to recover from a seizure or pai****n, what life is that?* ***There's zero quality of life there and I would not want him to suffer in that way.***" - Lindy, mother of a 14-year-old son living with Type 2A, late infantile GM1

Premature dying was the second-most selected worry

This worry is not surprising as GM1 has a relentless progression from onset, which eventually results in premature death. At the end of each year Cure GM1 creates a video remembering and celebrating the individuals with GM1 who passed during the year.

*"**Our worst days were difficulty breathing, not being able to tolerate feeds, many hard seizures, storming, restlessness from discomfort, fear of it being our last days but also hoping the pain would end**."*- Katie, mother of a child living with GM1

*"My biggest fear is that [our son] will **not have a long life and that in the meantime he will lose all of the abilities he has now**, basic abilities like eating and motor skills. I worry about everything that can happen with the disease, including **seizures** and **loss of all movement**."* - Abby, mother of a son living with Type 1, infantile GM1

*"I also feared **seizures in their sleep** and them **passing away in their sleep** due to seizures."* - Deborah, parent of sons with GM1 who passed away

Other worries selected in the polls: worsening symptoms and uncontrolled seizures, followed by the worry of their loved one being unable to communicate health problems, and impacts on family and social relationships.

Many of these worries are reflected in the quotes above. Although selected near the bottom of the polls, worries about the impacts on family and social relationships -- particularly the impacts on parents and siblings -- generated many comments.

After her granddaughter passed away from GM1, *"Now **my worries are about the mental health of my daughter, other granddaughters, son-in-law, other family members**, and the impact of this long-term on everyone."* – Tania, grandmother of a granddaughter with Type 1, infantile GM1 who passed away

Jenny worries about how her daughter's GM1 affects her older son. "*I have an 11-year-old son, and **to watch his sister, his only sibling, essentially slowly dying** and the impact that's going to have on him currently and in the future*." - Jenny, mother of an eight-and-a-half-year-old daughter living with Type 2A, late infantile GM1

Cindy described how GM1 has impacted her life. *"Our **whole world** that used to be really big just **got smaller and smaller and smaller and smaller**. You just start **eliminating things from your life** that your child is unable to do. And as you do that, **your world gets tinier**. Your interaction with people gets tinier."* - Cindy, mother of a 34-year-old son living with an unusual form of GM1 with both juvenile and adult-onset characteristics

Session 2: Current and Future Treatments for GM1

During the EL-PFDD meeting, parents and caregivers discussed all the different types of medications and medical therapies that they had used to manage their loved ones' symptoms and to give them some relief. Several had made the challenging decision to try gene therapies or other experimental therapies, with some reporting initial success. All GM1 patients receive a great deal of speech, physical, occupational, and other therapies, however, this only slows disease progression. They described all the downsides of the therapies, which in some cases were extreme. Parents selected what they felt were the most meaningful changes that they would like to see from a future therapy, the things that would best help preserve their children's quality of life.

Q1: There is an enormous unmet medical need for FDA-approved, disease-modifying treatments specifically for GM1 gangliosidosis

> *"Shortly after diagnosis, we learned **there is no official cure or treatment for GM1**, which is why we're here today."* - Tom, father of an 18-year-old daughter living with Type 2B, juvenile GM1

Parents and caregivers used online polling to select the many medications and medical treatments that their loved one used to manage symptoms associated with GM1. Each selected an average of 4.4 response options. Over the counter medications for pain, other medications including experimental therapies and breathing support, dietary or herbal supplements and melatonin and sleep medications were the top selected options, however none of them change the course of GM1. Poll results are shown in **Appendix 6, Q1** and illustrated below.

Other medical approaches including gene therapies, surgeries and oxygen/ventilators

Although "other medications" was the second most selected response option in the polls, gene therapies were discussed at great length during the meeting. Parents also described the role of surgery, ventilation/supplemental oxygen and mentioned scopolamine and other medications used to reduce oral and respiratory secretions.

Gene therapies are currently in clinical trials and some parents reported positive outcomes.

> Rachael's son's initial results were hopeful. "*There were some improvements in his cardiomegaly, which filled us with hope. Further to that, we were noticing that he was more active. He was grabbing toys and moving them around. … It has now been a few months since he received gene therapy and **there does not seem to be any side effects** from the actual treatment, **but the condition seems that it is still progressing**."* - Rachael, mother of a 10-month-old son living with Type 1, infantile GM1

> *"My son received intra-cisternal gene therapy two and a half months ago, and I already know it has given him **more years of quality life than he would have had without treatment**. Before the treatment, he was on a dramatic decline, rapidly losing skills and worsening quality of life. **Since treatment, regression stopped entirely and he has been able to regain skills like taking steps, eating solids, and increased vocabulary**. Even if it doesn't cure him, I would absolutely do this treatment again if given the chance."* - Stephanie, mother of a one-and-a-half-year-old son living with Type 2A late infantile GM1

Maria's youngest son was treated with IV gene therapy*. "He seems to be benefiting very much from the gene therapy. He's* ***still making developmental progress at age six****. He's in a* ***typical kindergarten classroom*** *with some supports for his fine motor struggles. And so obviously, we don't know how long those effects will last, but* ***the gene therapy really has been beneficial for him****. And I believe that's because he was treated so early."* - Maria, mother of 14 and six-year-old sons living with Type 2B, juvenile GM1

"Last June [my grandson] received a triple dose of gene therapy. When he is having a good day, ***he feels good****, he is very concentrated, he runs better and longer distances, his hands are not cramped and* ***his speech is clearer, he is more confident*** *and his balance is very good,* ***his fine motor skills are better developed****."* - Christina, grandmother of a kindergarten-aged boy living with GM1

Despite the promise, gene therapy has many downsides. Results can be variable, and at best may only halt progression but does not offer a cure. Opportunities for experimental therapies are extremely limited and they come with the risk of death. Eligibility requires an early diagnosis. The decision to enroll is both challenging and very emotional. Parents described how the treatment preparation was physically and emotionally gruelling and the post-therapy follow up is extensive. Explaining the testing and treatment to young children is challenging.

"Being only three months old, [our son] was one of the youngest diagnosed and this made him eligible for the clinical trials. Obviously, we opted to choose the ones which had the first opening, as we know time is of the essence for GM1 babies. ***It was not an easy decision****. On one hand, we knew that this was a clinical trial and not a cure, which maybe will not have any impact at all, but on the other hand,* ***we could not live with the regret of not giving him this chance****."* - Ronnie, father of a 10-month-old son living with Type 1, infantile GM1

Gene therapy in combination with intensive physiotherapy created a plateau for Jessica's daughter, including improvements to her fine motor skills, the ability to hold up her head, the ability to breathe. "***She seemed to be happier, more expressive for longer periods of time. … She would play with her toys****. She would hold our finger. She was able to drink orally from a bottle quite well for a longer period of time, which is a big deal. And that really improved her quality of life and improved our ability to connect with her as caregivers because we're able to hold her and feed her and have that connection and that time with her versus being fed with the G-tube…She plateaued for a while, and then* ***all of a sudden, she had a very rapid progression over a span of about one to two months. It was just a very quick decline****."* - Jessica, mother of a daughter with Type 1, infantile GM1, who passed away

Rojan found the decision to try gene therapy for her son difficult. "*We had to face the harsh reality that* ***a successful trial would be keeping him in his current state****. A three-year-old who can't walk or talk is still cute and physically manageable, but would he be at 20? Were we ready to be lifelong caregivers?* ***We also feared the safety of the treatment*** *since it was first in human, but truthfully, that risk wasn't as daunting since GM1 was going to take his life eventually. Ultimately, we decided we could not live with the regret of not trying if the trial ended up successful."* They saw a slight improvement in

his abilities, but six months after the therapy, their son *"suffered his first seizure, a major sign that the disease was progressing.* ***It's been three years since treatment, and unfortunately [our son] has regressed significantly****. Do we regret what we put him through? No, we had to try."* - Rojan, mother of a five-year-old son living with Type 2A, late infantile GM1

Niclas had to consider eligibility for all three of his children, whether any would be randomized to placebo, and the fact that gene therapy required the children to be immunosuppressed during a global pandemic. "*The gene infusion itself was unexpectedly uneventful, 25 minutes with an IV drip, and then done, but it was still a very emotional day for us. …****After treatment, the disease stabilized significantly, but we're still struggling with managing three children with GM1. Mentally, they're all like three-year-olds****."* - Niclas, parent of three children living with Type 2A, late infantile GM1

"Even though [my grandson] had the gene therapy, ***his regression has progressed dramatically in the last year****. When he was treated, he could still hold his own sippy cup and drink and he could sit up and roll. And now we've lost all of that."* - Martha, grandmother of a grandson living with Type 2A, late infantile GM1

Surgeries. Parents and caregivers described how their loved ones received hip replacements, scoliosis surgeries, G tube placements, gall bladder removal and adenoid surgery.

"[Our daughter] had her ***tonsils and adenoids removed*** *and grommets fitted and although* ***the drooling slightly improved, it did not stop****."* - Ryan, parent of an eight-year-old daughter living with Type 2B, juvenile GM1

Supplemental oxygen and machines to support breathing. This includes ventilators, BIPAP machines, oxygen monitors, and cough assist and suctioning to clear secretions.

"*Breathing was her biggest difficulty. We used* ***cough assist*** *and* ***suctioning*** *as her disease progressed, … about every hour. She used* ***BIPAP at night****, and that also helped give her more energy during the day because* ***she did have sleep apnea*** *where her brain would forget to breathe at night. …Once we started using the BIPAP, we noticed* ***how much easier she could breathe on her own during the day and how it helped her lungs become stronger****, which was a big positive."* - Jessica, mother of a daughter with Type 1, infantile GM1 who passed away

Abby's son requires **supplemental oxygen** and uses an **Owlet monitor** because of aspiration. *"When we are at home, he is hooked up to an* ***oxygen concentrator****, which means he has roughly 20 feet to move around in. This prohibits me from moving around the entire house as needed very easily."* - Abby, mother of a son living with Type 1, infantile GM1

Over the counter medications (acetaminophen, ibuprofen), dietary or herbal supplements and melatonin and sleeping medications

The poll results indicated that over three-quarters of the individuals living with GM1 use OTC medications, almost two thirds have tried dietary and herbal supplements and over half have used melatonin and sleep medications. A downside is that they don't always work well.

> *"We used **a lot of different herbal and other type supplements** to really **help with bowel regularity**. That was an issue and spitting up and all of that digestive stuff to help keep them as comfortable as possible. …We would use **magnesium citrate** to just kind of get it going. And then we had other things that we just did on a regular basis as well, and **I tried not to do too many enemas** to artificially …. Just tried to help in other ways to get it going, and then I would use if I needed to."* - Marilee, mother of three children diagnosed with Type 2A, late infantile GM1, including two who have passed away

> "*He does take **melatonin**, and that **helps him get to sleep**. But that **doesn't help him stay asleep**."* - Maria, mother of 14 and six-year-old sons living with Type 2B, juvenile GM1

Anti-seizure medications

Almost half of individuals living with GM1 have used seizure medications including Keppra, Topamax, Epidiolex, Banzel (rufinamide), many of these in combination. It can take a long time to identify the best medication or the best combination of medications. Seizure medications can cause extreme side effects.

> David and his wife, who are both physicians, had a challenge finding a combination of seizure medications to reduce seizures and improve their daughter's quality of life. *"We actually started her initially on **Keppra and Topamax**, which are pretty standard anti-seizure medications. And those were okay. But **the addition of Epidiolex as a third part of the regimen actually helped dramatically**."* - David, father of an infant daughter living with Type 2A, late infantile GM1

> *"For a couple years, she could have over **100 seizures in any given day** until **Epidiolex and Banzel medicine** helped bring those **much more under control**. The two-year journey of finding **the right seizure medicine** has left her with **only five teeth on top**."* - Douglas, father of a 14-year-old girl living with Type 2B, juvenile GM1

Acetyl-DL-leucine (Tanganil), prescription medications for muscular issues (Baclofen, diazepam, Dysport), medical marijuana and cannabidiol (CBD)

Acetyl-DL-leucine is an anti-vertigo medication that assists with motor skills and speech and was selected by over a third of parents and caregivers in the polls. Prescription medications for muscular issues were selected by a quarter of parents and caregivers, and some described using Botox for muscular issues.

> "*Thanks to the **Botox shots**, she's getting a **little bit of relief** on her right leg and is able to **walk in her gait trainer**."* - Ruth, mother of a 20-year-old daughter living with Type 2B, juvenile GM1

> *"I thought Botox helped my son. He was receiving **Botox every three months for over two years**. Hasn't been for Botox treatment for two years due to Covid, and **I see no difference**."* - Arlene, mother of a 33-year-old son living with Type 2 GM1

Medical marijuana, cannabidiol (CBD) and Epidiolex were selected in the polls by over 20% of parents and caregivers. Of these, only Epidiolex was discussed in the context of seizure control (above).

Miglustat (Zavesca) and other substrate reduction therapies

While approved by the FDA for the treatment of mild to moderate type 1 Gaucher disease, miglustat is also used off-label for the treatment of other lysosomal storage disorders. Similar medications, including venglustat and eliglustat (also approved for Gaucher disease), are in clinical trials. For some parents, these medications worked well.

> Ryan's daughter is enrolled in a clinical trial for venglustat. "*This drug is a **substrate reduction therapy**, which we hoped would slow down or even freeze the progression of the disease. …Two weeks after her first dose, **we started to see positive change**. [Our daughter] started to walk flatter footed. Her **speech became clearer** than before and her **drooling stopped**. … Over the next few months, **improvements continued**. …Fifteen months on from her first dose, we have seen no obvious side effects. She is developing well and from what we can see, there has been **no more disease progression**. This very small tablet has been a lifeline for [our daughter] and has changed our lives."* - Ryan, parent of an eight-year-old daughter living with Type 2B, juvenile GM1
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> *"Our daughter takes the specialty drug **miglustat in conjunction with a ketogenic diet** needed to subdue the side effects. This particular treatment for lysosomal storage disorders in theory may help her molecular cells process beta-galactosidase more efficiently to slow down progression."* - Tom, father of an 18-year-old daughter living with Type 2B, juvenile GM1
>
> Cindy's son started taking miglustat off-label. "*My son **had a dramatic response**. I mean, this was a child who was sitting in a wheelchair in almost like a catatonic state. Once he started taking miglustat, it was **miraculous how he came back to us**. I mean, **he started interacting again**. He started doing play with his little characters and his toys again, and he started getting down on the floor and **wanting to crawl** around again. For us, **it was a miracle drug**.*" - Cindy, mother of a 34-year-old son living with an unusual form of GM1 with both juvenile and adult-onset characteristics

Some parents reported GI side effects.

> David's daughter discontinued miglustat for gastrointestinal issues. *"We were recently enrolled in a clinical trial for the other small molecule, **venglustat**, which she's been **tolerating much better**. So that does **give us some hope** that perhaps the benefits seen in miglustat would be seen on venglustat **without the same side effect profile**."* - David, father of an infant daughter living with Type 2A, late infantile GM1
>
> *"Medication **side effects of miglustat** include **gastrointestinal symptoms** that often present themselves unexpectedly."* - Tom, father of an 18-year-old daughter living with Type 2B, juvenile GM1

Pain medications (morphine, oxycodone)

Almost a quarter of parents and caregivers have used pain medications including morphine and oxycodone. They also described using other pain management approaches including gabapentin for neuropathic pain and trying to distract their children from their pain.

> "*[Our daughter] will have days where she will be **crying and screaming in pain for 8, 10, 12 hours** with very few breaks in between. And she can't tell us what's wrong, so*

*you have to guess. …We've had some great help from **palliative care and other doctors** who have helped get her on some medications that have really seemed to **give her some relief**, so those days are few and far between now, which is great*." - Matt, father of a five-year-old daughter living with Type 2A, late infantile GM1

*Gabapentin made an enormous improvement in Maria's son's life. "We struggled for a while with him just getting **progressively fussier and fussier**. He was whining a lot. He was just **not the happy kid** that we used to know. …We didn't know if it was just neurological, he just wasn't understanding things or if it was **pain related**. He has some of the skeletal issues that are common in GM1, and we weren't sure if he was having pain. …**Gabapentin has really seemed to make a difference in how rested he is in the morning**. And his mood is just happier. …**He is just overall much happier** now. …. It has just made a huge difference in his quality of life."* - Maria, mother of 14 and six-year-old sons living with Type 2B, juvenile GM1

Q2: All individuals living with GM1 rely on a combination of different therapies, strategies and adaptations, which change as the disease progresses

Parents and caregivers used online polling to select all of the different therapies, strategies and approaches that they have used to help manage their loved ones' GM1 symptoms, and each respondent selected an average of 6.5 responses. Results are shown in **Appendix 6, Q2**. Most described how they used combinations of many different therapies and adaptions, which changed as the disease progressed.

Physical, occupational and speech therapies were the top selected therapy approaches

All individuals living with GM1 receive physiotherapy to help maintain muscle function, and many receive this in combination with occupational therapy which helps develop/maintain fine motor function as well as speech therapy to assist with both communication and eating. Several also mentioned swim therapy, riding therapy and other animal-based therapies. Most require these therapies many times each week and some receive them through their school individual education plan (IEP).

*"We did an **intensive type of physiotherapy** ... it is not very pleasurable for the children, but they do have **drastic results** from it. And we definitely did notice that, in combination for [our daughter] in the first few months of her gene therapy, created a plateau for her."* - Jessica, mother of a daughter with Type 1, infantile GM1 who passed away

"*I believe that the **physical therapies** and the **occupational therapies, aqua-therapies**, were really **our biggest friends**."* - Martha, grandmother of a grandson living with Type 2A, late infantile GM1

Tom's daughter receives physical, occupational, and speech therapy for several hours each week at home and through her school IEP. "*She receives p**hysical therapy to try and maintain mobility** as GM1 continues to devastate her neurology and muscle function. …She also gets **occupational therapy*** through craft activities *to provide a creative outlet while trying **to maintain what fine motor skills** she has remaining. …She also received **speech therapy** to try and maintain not only what **linguistics***

capability *remain, but also for nourishment by* ***maintaining her ability to eat****."* - Tom, father of an 18-year-old daughter living with Type 2B, juvenile GM1

"She does ***hydrotherapy, hippotherapy, speech therapy****, and* ***physiotherapy****, because she has* ***scoliosis****. I am very anxious waiting for possible treatments or genetic tests for her because she is* ***regressing***." - São, mother of a 14-year-old daughter living with Type 2B, juvenile GM1

"*He has many therapies every week such as* ***ergotherapy, speech therapy****,* ***physiotherapy, riding therapy****, he goes to a* ***farm where he deals with animals therapeutically****. He likes going to the animals best. He loves the sheep, cows, chickens, cats, and dogs. They give him a lot and have a* ***positive effect on his health****."* - Christina, grandmother of a kindergarten-aged boy living with GM1

Mobility aids (walker, wheelchair, stroller)

Mobility aids are required by more than three-quarters of individuals living with GM1, especially as the disease progresses. Mobility aids and other supports can be expensive.

"*We created a foundation for her, and thanks to the good willing people's donations, we could buy her* ***professional equipment*** *like a* ***special bed, bathtub, pram, proper monitoring system*** *to see her blood oxygen level, heart rate, and her whole status and other useful keys to* ***improve her life***." - Bence, father of a two-year-old girl living with Type 1, infantile GM1

Ankle foot orthotics/hand braces/back braces as well as other equipment and adaptations

Some individuals with GM1 absolutely rely on many types of supports and mentioned their requirements throughout the meeting.

Marilee's oldest son also had a back brace to help his kyphosis in his lower spine. *"Those back braces … I felt like did* ***more harm than good*** *and* ***didn't help at all with the situation****, at least in our case. It just made it* ***harder for him to walk*** *and avoid falling because he was so stiff. … And it just made it* ***more dangerous****. We did give it a good effort. Didn't notice any improvement there."* - Marilee, mother of three children diagnosed with Type 2A, late infantile GM1, including two who have passed away

Equipment requirements changed at different disease phases. Marilee described how in the early stages of GM1, her children required helmets, knee pads, and bum pads when they started to fall down. In the middle stages, her children needed feeding tubes, wheelchairs, other mobility aids, and thick towels to help with the drooling. In the final stages, before her children passed away at ages 10 and 11, they needed a *"****more peaceful environment*** *because they tended to be so much more scared,* ***more medications to support****."* - Marilee, mother of three children diagnosed with Type 2A, late infantile GM1, including two who have passed away

Feeding therapy

Individuals living with GM1 used feeding therapy to maintain their ability to eat with their mouth, yet this is still a struggle and some parents have to puree their loved one's food. Eventually, a

G-tube is necessary to help maintain their nutrition and hydration, and even that necessitates adaptations including bolus feedings.

> *Martha explained how feeding therapy works. "We work with **tools to help his chewing mechanisms**, and even though he doesn't chew, it strengthens that **moving the tongue** and **moving the food to the back of his throat** so **he can swallow better**. [Feeding therapy] has been a great help to us because we have, up to this point, avoided a G-tube."* - Martha, grandmother of a grandson living with Type 2A, late infantile GM1

> *"The **feeding tube was great for us for a few years**, but you're kind **of force feeding the body** with maybe what they're not really able to tolerate **as the disease progresses**, so you have to really be watching that."* - Marilee, mother of three children diagnosed with Type 2A, late infantile GM1, including two who have passed away

> After Douglas's daughter had her feeding tube installed, *"One of the parents suggested **bolus feedings once an hour**, which finally stopped [her from vomiting]. Now she's **gained her weight back** and 15 pounds more."* - Douglas, father of a 14-year-old girl living with Type 2B, juvenile GM1

Other approaches selected in the polls

The other approaches mentioned in the polls included assistive speech devices, Hensinger head support or other head or neck supports, general diet modification (gluten free, lactose free), complementary therapies (homeopathic, acupuncture), and ketogenic diets. Some mentioned how ketogenic diets were used in combination with substrate reduction therapies.

Approaches not mentioned in the polls – special education programs

During the meeting parents described other approaches including special education programs and social programs at school.

> Christina's grandson is excited to start school. *"He will be **supported at school by a school companion** who will support him if he needs help."* - Christina, grandmother of a kindergarten-aged boy living with GM1

> *"[Our daughter] has been enrolled in a **special education program** where she is able to use a **gait trainer** and an **adaptive tricycle**. This has given her a **sense of independence and normalcy**. We can see the pride on her face when she's walking and pedaling her bike. She feels **strong and proud**."* - Megan, mother of a five-year-old daughter living with Type 2A, late infantile GM1

> *"She participates in the **Best Buddy Program** through her school to have a **social outlet with peers**."* - Tom, father of an 18-year-old daughter living with Type 2B, juvenile GM1

Q3 & Q4: Current GM1 treatment approaches only treat some, not all, of the symptoms, are not very effective, and are limited in availability/accessibility

Parents and caregivers used online polling to first indicate how well their current treatment regimen treated the most significant symptoms of GM1, and then to select the top three drawbacks of their loved one's treatment regimen. Poll results are presented in **Appendix 6, Q3**

and **Q4** with patient quotes. None of the poll respondents indicated that they did not use any therapy.

Only treats some not all symptoms and is not very effective at treating target symptoms

These were among the top drawbacks selected by parents and caregivers and are consistent with the results of poll Q3, where most parents indicated that their current regimen only helps "somewhat" or "very little". The lack of effective treatments for GM1 was a message reinforced throughout the meeting. Even if a medication or treatment approach helps to give relief from one symptom, the disease keeps progressing.

> *"I would say treatment regimen **helps somewhat** because we are **fighting a losing battle**. We certainly **need all of the equipment**. We definitely use **physical therapy, orthotic braces, Baclofen**, and **Botox injections** to help with **muscle tightness**. The **medications** help with **keeping her bowels moving**, **combating motion sickness** and **excess drool** (which she often aspirates due to loss of swallow reflex), and **assisting with sleep**. But **every time we get one thing under control, something else develops**."* - Honey, aunt of a niece living with Type 2A, late infantile GM1

Limited availability or accessibility

The results of poll Q3 showed that some parents and caregivers selected that their current treatment regimen worked to a great extent to treat the most significant symptoms of GM1. They previously described how gene therapy, experimental therapies, extensive physiotherapy, and other therapy approaches have helped to maintain their children's abilities, however, there are challenges in consistently obtaining these medications and therapeutic approaches.

Clinical trial access is extremely limited due to eligibility criteria favoring younger, recently diagnosed children, and those with specific disease characteristics and a clearly defined GM1 subtype. Some reported feeling devastated about not meeting trial eligibility and some just live too far from a clinical trial site to participate. Parents of older children felt that their children were excluded from trying therapies that were likely to have some benefit.

> *"**A trial gave hope**, then they **weren't selected** and they were **back to devastation**. They are **currently in fight mode** but have bad days and **feel desperate**."* - Heather, friend of a caregiver

> *Some of us who have older children with GM1 are really frustrated by the fact that none of the clinical trials or the treatment options that are being trialed are open to older kids. …A lot of the drug companies are opening those only to younger children or infantile form. …**It's frustrating for older patients to have no treatment options available to them** and to not even be considered for the trial."* - Cindy, mother of a 34-year-old son living with an unusual form of GM1 with both juvenile and adult-onset characteristics

Some are trying desperately to maintain access to medications as their trial comes to an end.

> *"With the trial due to end within the next year, our attention now turns to being able to **continue to access the drug**. We are investigating if a **trial extension** or **approval** may happen or if **compassionate access** could be considered."* - Ryan, parent of an eight-year-old daughter living with Type 2B, juvenile GM1

Many parents indicated that the physiotherapy, occupational, and speech therapy are only available/accessible through individual education plan (IEP) programs at school, and as children "age out" of programs, they lose access. Many also mentioned how therapies were limited during the COVID-19 pandemic.

> *"While we have done our best without any additional support for medical treatment, services, or equipment after 18 years, it is clear* ***our daughter is losing the race against time for a cure****. A significant* ***reduction in her capabilities*** *resulted over the past two years as she was* ***unable to receive IEP services due to the pandemic****.* ***She'll soon be permanently disabled because of the lack of serious, meaningful and effective treatments****."* - Tom, father of an 18-year-old daughter living with Type 2B, juvenile GM1

Requires too much effort or time commitment

This downside was mentioned throughout the meeting with regards to physiotherapy and other therapies that are required.

> *"While other parents are taking their children to soccer practice and dance, we are taking [our daughter] to* ***outpatient therapies****,* ***hippotherapy****, and* ***working tirelessly*** *to keep her strong to fight GM1."* - Megan, mother of a five-year-old daughter living with Type 2A, late infantile GM1

> *"As an adult, she understands more that she has to take care of her body, although she is* ***burned out from being in therapy for so many years*** *and sometimes she leaves because she is* ***mentally exhausted****, although after a while she reconsiders and resumes her therapies."* - María José, mother of a 20-year-old daughter living with Type 3, adult onset GM1

Clinical trials especially require a great time commitment.

> Ronnie described all the tests his son required prior to starting **gene therapy**, including, "*An* ***MRI scan****,* ***echo test****,* ***audiology****,* ***ophthalmology****,* ***lumbar puncture****,* ***occupational therapy****, and* ***physiotherapy****."* – Ronnie, father of a 10-month-old son living with Type 1, infantile GM1

> Rojan's son was one of the first to receive **gene therapy**. *"[Our son] underwent* ***two weeks of grueling procedures and exams in preparation*** *for the [clinical trial] treatment."* - Rojan, mother of a five-year-old son living with Type 2A, late infantile GM1

> Although Marilee would definitely have her child participate in a trial again, she cautioned others about the intense time and emotional commitment. "***It is intensive****. There's a lot of* ***repeated visits****, especially when you're* ***traveling a far distance****. …You're having to do all these things in an* ***intensive, short period of time****, all these* ***different tests****, it can be* ***hard on the rest of the family****. But now that our other two children have passed away, it's a lot easier for our family to manage going. Now we can go together, and we can support one another in this."* - Marilee, mother of three children diagnosed with Type 2A, late infantile GM1, including two who have passed away

Side effects

Several parents described how the side effects forced them to continue treatments for their children.

> *"**Miglustat was tolerated initially okay**, but unfortunately, it did come with **a lot of GI side effects**, **a lot of gas and diarrhea** to the point where we almost got afraid of her being **dehydrated** and actually needing IV fluids. …Whatever improvements we could have seen were probably offset by the fact that she was **dehydrated** and **not having a good time with the medication itself**."* – David, father of an infant daughter living with Type 2A, late infantile GM1

Side effects were particularly severe for Douglas' daughter, who experienced vomiting and extreme gum swelling resulting in the loss of most of her teeth.

> *"The **one seizure medicine** s**welled her upper top gums so much, they burst the teeth off her skull**. After four **panic filled days** and a few misdiagnoses, **I stopped the seizure medicine**. The gum swelling stopped, but **most of the teeth couldn't heal** and **fell out**.* - Douglas, father of a 14-year-old girl living with Type 2B, juvenile GM1

Sometimes side effects of one medication can make another symptom worse, making it harder to select appropriate treatments.

> *"Some of the **treatments for one symptom exacerbate other symptoms**. For example Scopolamine, used for motion sickness and to reduce drooling, **exacerbates my child's constipation**."* – Jenny, mother of an eight-and-a-half-year-old daughter living with Type 2A, late infantile GM1

Other drawbacks selected in the polls

These include the number of pills/medications/preparation as well as the high cost or co-pay, not covered by insurance.

> *"In addition to the above, **he's taking various medications**, **some of which he takes without complaints. Others, he does not really enjoy**, but we believe that all we are doing is to make his life as comfortable as possible, whilst hoping that gene therapy has worked on him."* - Rachael, mother of a 10-month-old son living with Type 1, infantile GM1

Other drawbacks not mentioned in the polls

These include the invasive administration options for gene therapy, and a lack of understanding of this disease in the medical community which makes it hard to obtain appropriate treatment.

> *"My son had **breathing issues** from the beginning and **couldn't even go under to get his pic line changed sides**. So **invasive surgeries [for the gene therapy administration] wouldn't be an option**."*- Nolan, parent of a child with type 1 infantile GM1 who passed away

> *"Significant downsides of treatment include **most medical professionals who have no idea what or how to deal with GM1 patients** and frequently **it is a struggle to get***

***them to collaborate**."* - Tom, father of an 18-year-old daughter living with Type 2B, juvenile GM1

Q5: Short of a complete cure, parents would like a slowing or stopping of disease progression. However, any therapy that improved quality of life is welcome

Parents and caregivers used online polling to select the top three things they want in an ideal GM1 treatment. During the meeting, many parents emphasized how much they wished for a cure, and short of a cure they selected slowing or stopping of the disease, followed by lessening of pain, improving expressive communication and improving cognitive functioning. Poll results are in **Appendix 6, Q5**.

Slowing or stopping disease progression

A treatment to slow or stop disease progression was the overwhelming first choice of parents and caregivers.

> "*If we could just put a **pause or slow down everything**, that would be ideal*." - Maria, mother of 14 and six-year-old sons living with Type 2B, juvenile GM1

> *"I wish I could at least **arrest the disease** to **avoid the horrible conditions** that arise as the condition progresses. Please help us parents, help our children and adults to give them some relief!"* - Ruth, mother of a 20-year-old daughter living with Type 2B, juvenile GM1

> Martha specifically wants the progression stopped, not slowed. "*I would choose **either stopping it or nothing**. …**I don't want it slowed down**. …**I don't want to prolong it**, because [my grandson] does struggle*." - Martha, grandmother of a grandson living with Type 2A, late infantile GM1

Lessening of pain, improving expressive communication and improved cognitive function

Lessening of pain was not a surprising second choice, as so many parents spoke about their loved ones' uncontrolled pain throughout the meeting. Improved expressive communication and improved cognitive function were also highly ranked.

> *"If I had to pick, I'd **wish she could find peace and contentment**. I wish she **no longer had a pained look on her face** much of the day. **I want her to be happy**."* - Douglas, father of a 14-year-old girl living with Type 2B, juvenile GM1

> "***Communication and speech is huge**, but even if a child loses their speech, if they still have a high level of cognition, **there are other ways that they are able to communicate** via **speech devices and eye gaze systems** and such*." - Maria, mother of 14 and six-year-old sons living with Type 2B, juvenile GM1

Increasing lifespan - but with an important caveat about quality of life

Increasing lifespan was selected by a quarter of parents and caregivers. However, both in the meeting and in the Caregiver Study, parents and caregivers emphasized that they would not increase lifespan at the expense of quality of life.

*"And our main focus is **quality of life** for [our grandson], **not necessarily quantity, but quality**."* - Martha, grandmother of a grandson living with Type 2A, late infantile GM1

*"We fight until our little [daughter's] last breath and even though we know that one day death would come... for her general well-being, for her comfort and **we did everything in our power for her to have quality of life**."* - Joslane, parent of daughter living with GM1

In the Caregiver Study, parents prioritized the symptoms they believed would increase their child's lifespan and improve their quality of life. Although lifespan was very highly valued, almost all parents would not desire a longer life without associated high quality of life for the child. Parents described quality of life as maintaining at least modest cognitive abilities, absence of pain, and comfort and happiness. Thus, parents prioritized the symptoms they believed would achieve this objective, focused on the ability to communicate wants/needs, prevent pain/discomfort, improve ability to get around, and enhance eating/feeding.

Other treatment wishes selected in the polls

Decreasing seizures, improved ability to swallow, improved sleep, improved mobility and coordination and improved receptive communication were all selected. These are reflected in the comments below.

"*To me, **if gene therapy stopped the seizures, I would consider that a huge success**. If a life without watching my son twitch and turn blue for minutes at a time was achievable through the treatment, I would endure those 10 weeks all over again*." - Rojan, mother of a five-year-old son living with Type 2A, late infantile GM1

*"The **lessening the seizures** for me, …that's an important one for me because we are having trouble managing those."* - Martha, grandmother of a grandson living with Type 2A, late infantile GM1

"*To me, finding a cure or some way of **stopping the rigidity** would be great, because it's **so hard to get her dressed** and to get her to **raise her arms** or **give me her foot**. Even to feed her now, I can see that she's **having trouble moving her tongue** from side to side or **being able to chew the food**. I have to cut it so small and find foods that she's able to actually swallow, with the fear of one day, **she will have to have a G-tube***." - Ruth, mother of a 20-year-old daughter living with Type 2B, juvenile GM1

"***Mobility is really important** too, to be able to **do what they want** and **get in the positions** that they want and **get around** is very important*." - Maria, mother of 14 and six-year-old sons living with Type 2B, juvenile GM1

Other treatment goals not listed in the polls

Parents mentioned other therapeutic considerations during the meeting, including greater accessibility to treatments for older patients and for those with more advanced disease, and the flexibility to try combinations of treatments.

"We also wish that research would ***expand human clinical trials*** *to* ***include all patients*** *to ensure* ***the cure is available for all ages***. - Tom, father of an 18-year-old daughter living with Type 2B, juvenile GM1

Clinical trials to include patients with advanced disease. "*Clinical trials for GM1 have been including only children who have mild symptoms or are pre-symptomatic. There are many parents of children with a* ***more advanced stage of GM1 who would like the opportunity of trying some kind of treatment****. They realize the risks, but* ***the alternative is simply watching their children regress & waiting for them to die****. Since GM1 is universally fatal, giving them even a long shot of* ***a chance to improve their quality of life*** *should be available*." - Melinda, grandmother of a granddaughter living with Type 2A, late infantile GM1

"*I really believe that there needs to be* ***more options for parents to be able to try different things****. ...I think that gene therapy or small molecule therapy are not going to be enough. We're probably going to need those two things together to be able to impact and take this disease on because it is so severe. So****, the faster that we can have access to try different things and use those things together, the faster that hopefully we can start to chip away at being able to do something****. Because right now our community has absolutely nothing*."- Jessica, mother of a daughter with Type 1, infantile GM1 who passed away

Hopes for the Future for Those Living with GM1

The hope of the GM1 community is that the October 14th EL-PFDD will inspire future research and successful new product development for people living with GM1 who urgently need safe and efficacious treatment options.

> *"We hope that in a few years time, what we are doing today will result in* ***a cure for these children****, and if at least* ***this will not save our son, maybe it'll save others in the future*** *and every child will have the opportunity to receive treatments to save their lives."* - Ronnie & Rachael, parents of a 10-month-old son living with Type 1, infantile GM1

> *"We really* ***hope that there will be a cure in the future to this horrible disease*** *and* ***no other family needs to suffer****. There must be a solution*."- Bence, father of a two-year-old girl living with Type 1, infantile GM1

> *"Hoping does not mean that we ignore reality.* ***Hoping means we acknowledge reality****, and yet in the very same breath,* ***we acknowledge the promises of a future without pain or suffering.****"* - Megan, mother of a five-year-old daughter living with Type 2A, late infantile GM1

> *"****These kids are so resilient*** *and teach us so much every day to* ***be strong,*** *to* ***be happy in spite of all their trials and pain****."* - Ruth, mother of a 20-year-old daughter living with Type 2B, juvenile GM1

Incorporating Patient Input into a Benefit-Risk Assessment Framework

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

Table 1 summarizes the challenges of living with GM1 gangliosidosis. It serves as the proposed introductory framework for the Analysis of Condition and Current Treatment Option to be adapted and incorporated into the FDA's Benefit-Risk Assessment. This may enable a more comprehensive understanding of this unique condition for key reviewers in the FDA Centers and Divisions who would be evaluating new treatments for GM1. The data resulting from this meeting may help inform the development of GM1-specific clinically meaningful endpoints for current and future clinical trials, as well as encourage researchers and industry to investigate treatment options.

The information presented captures the perspectives of patients living with GM1 presented at the October 14, 2022, meeting. It includes information from the Caregiver Study and polling results, as well as comments submitted before, during, and after the meeting through the online portal.

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

TABLE 1 GM1 Gangliosidosis Benefit-Risk Table

	EVIDENCE AND UNCERTAINTIES	CONCLUSIONS AND REASONS
ANALYSIS OF CONDITION/ IMPACTS ON ACTIVITIES OF DAILY LIVING	**GM1 gangliosidosis is a neurodegenerative disease which progressively destroys nerve cells in the brain and the spinal cord**. After a period of normal development, children and adolescents living with GM1 regress and start to lose all their abilities. **All individuals living with GM1 are profoundly affected and many experience a great deal of pain.** The most troublesome symptoms, experienced by all, include regressions, impaired/loss of mobility, communication impairment, and cognitive impairment. Individuals living with GM1 also experience many other symptoms.	**GM1 has a relentless progression from onset, which eventually results in premature death**. **Patients are entirely dependent on their caregivers for almost everything.** They become unable to move and communication is impaired. **Parents experience many worries for their loved ones, especially about their diminishing quality of life.** In addition, parents worry about uncontrolled pain, premature death, worsening symptoms and uncontrolled seizures.
CURRENT TREATMENT OPTIONS/ PROSPECTS FOR FUTURE TREATMENTS	**Medications are required to help manage GM1 symptoms, but they do not halt disease progression.** These include medications for pain, sleep, and seizure management. **Patients living with GM1 require intensive physical and occupational therapy and extensive amounts of equipment for support**. This includes supports for breathing and feeding. Current GM1 treatment approaches only treat some, not all, of the symptoms, are not very effective, and availability/accessibility is limited. Most importantly, the disease still progresses. **Many have invested hope in experimental therapies including gene therapy**. Experimental therapies are not accessible to all, they often depend on early diagnosis, come with great risk and outcomes are variable.	**Treatments for people living with GM1 are urgently and desperately needed.** There are no FDA-approved treatments for any of the GM1 disease manifestations. **Short of a complete cure, parents would like a slowing or stopping of disease progression.** Parents emphasised that almost any improvement to quality of life would be welcome.
	See the Voice of the Patient report for a more detailed narrative.	

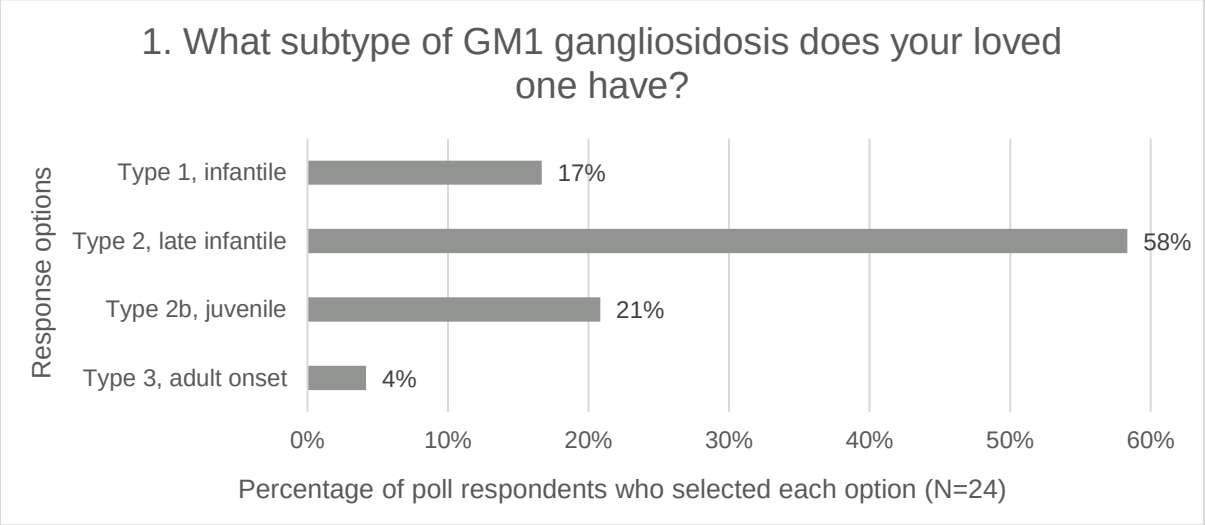
Appendices

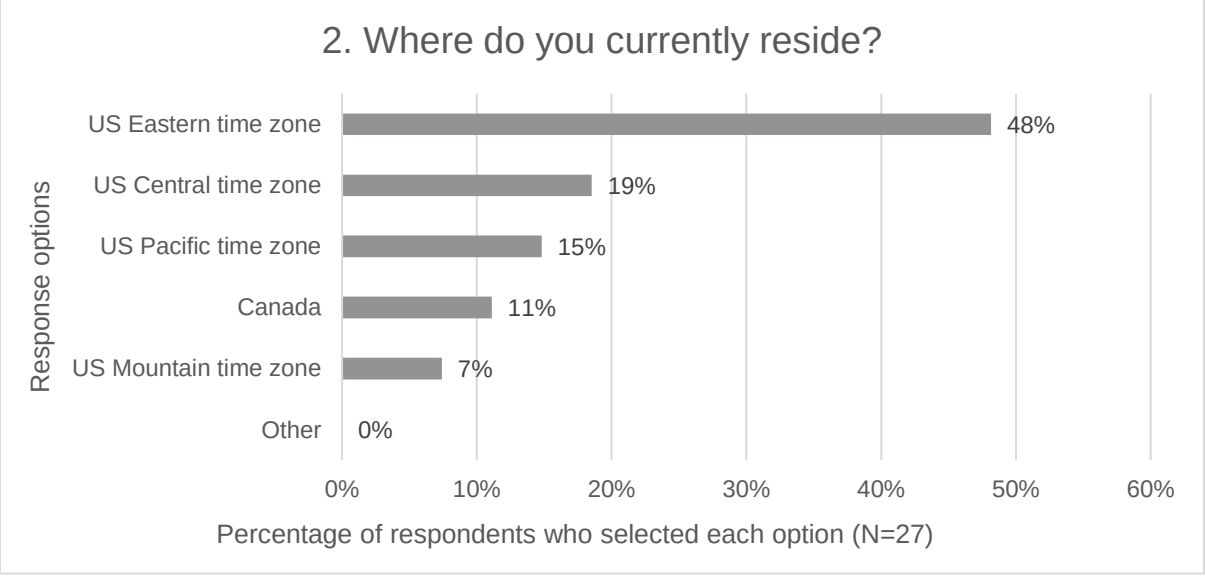
Appendix 1: Meeting Demographics - Polling Questions

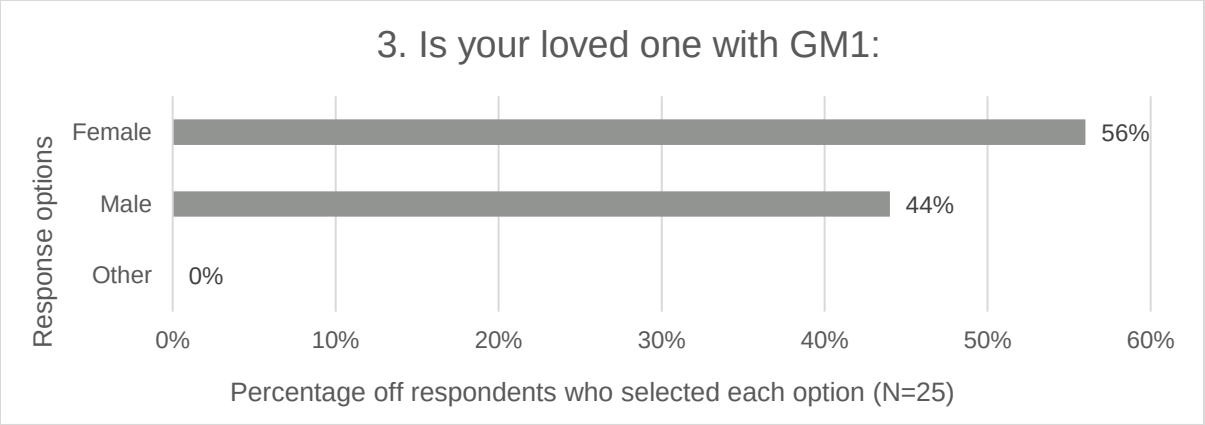
The graphs below include all meeting attendees who chose to participate in online voting.

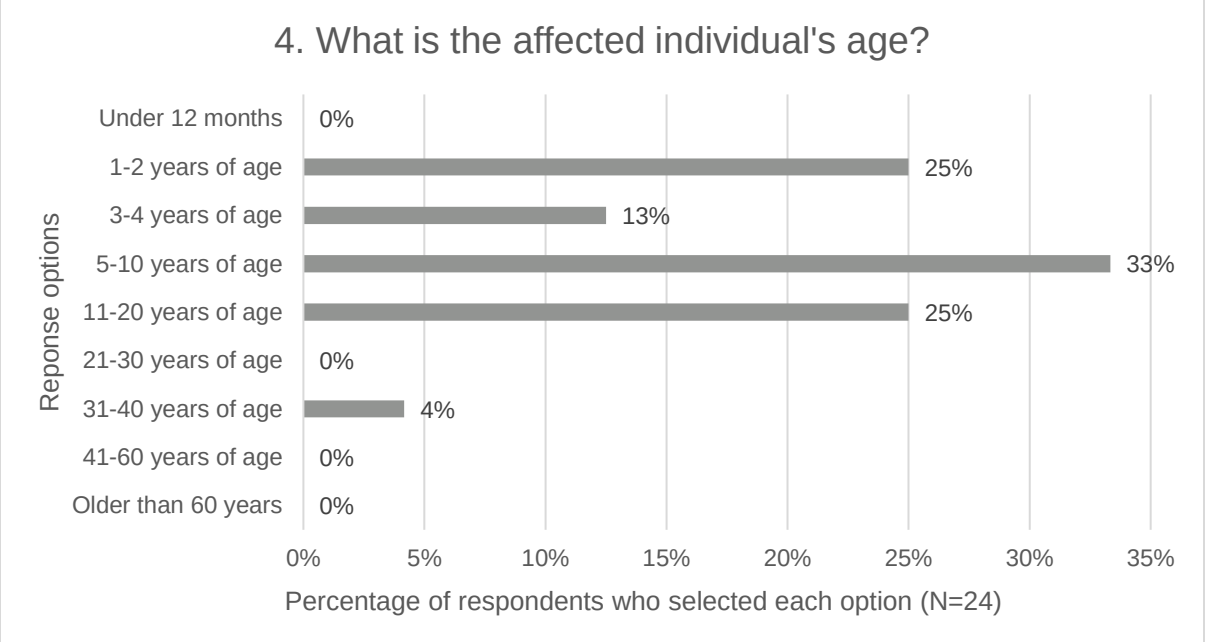
Parents and caregivers were asked to answer the questions on behalf of the individual living with GM1. The number of parents and caregivers who responded to each polling question is shown below the X axis (N=x).

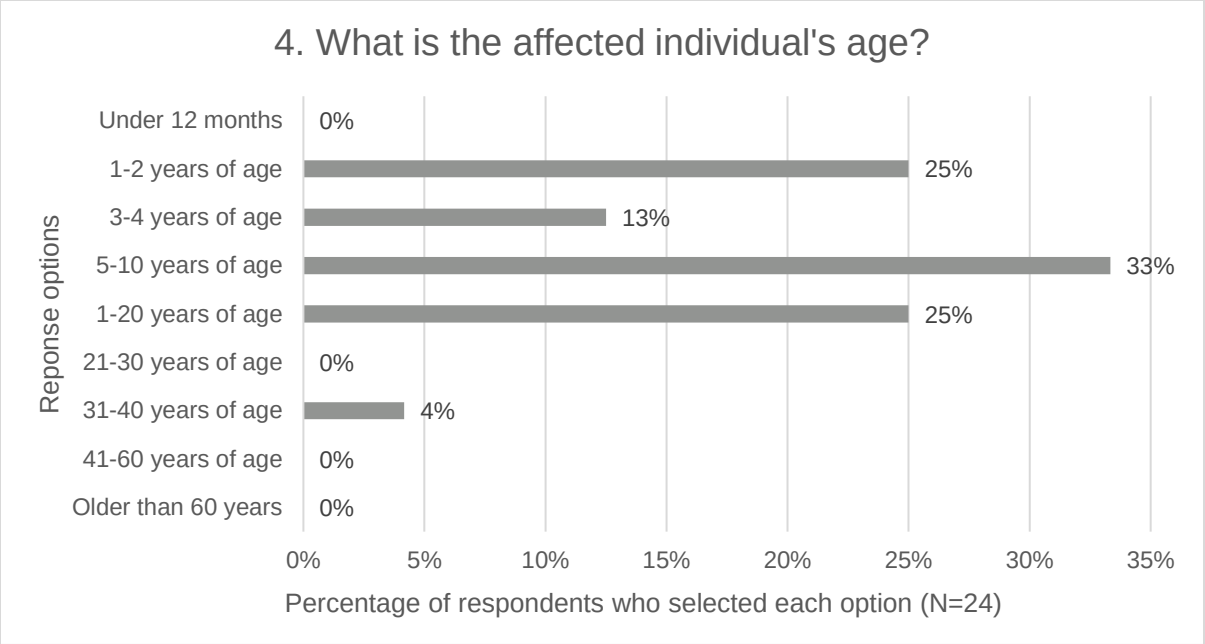
This information provides a snapshot of those who participated in the GM1 EL-PFDD meeting and is intended to complement the patient comments made during and after the meeting.

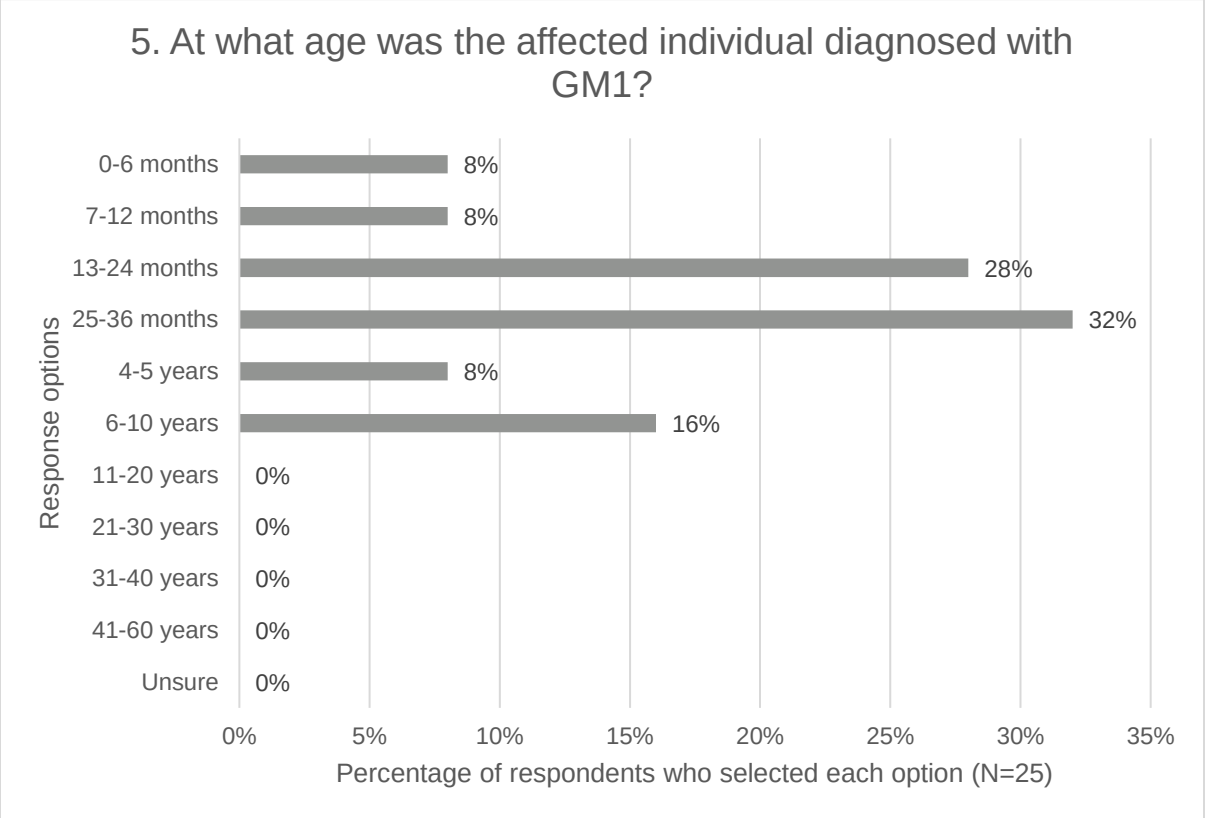





3. Is your loved one with GM1:
Response options
Female
Male
Other
56%
44%
0%
0%
10%
20%
30%
40%
50%
60%
Percentage off respondents who selected each option (N=25)


4. What is the affected individual's age?
Reponse options
Under 12 months
1-2 years of age
3-4 years of age
5-10 years of age
11-20 years of age
21-30 years of age
31-40 years of age
41-60 years of age
Older than 60 years
0%
25%
13%
33%
25%
0%
4%
0%
0%
0%
5%
10%
15%
20%
25%
30%
35%
Percentage of respondents who selected each option (N=24)


4. What is the affected individual's age?
Under 12 months
1-2 years of age
3-4 years of age
5-10 years of age
1-20 years of age
21-30 years of age
31-40 years of age
41-60 years of age
Older than 60 years
0%
25%
13%
33%
25%
0%
4%
0%
0%
Reponse options
0%
5%
10%
15%
20%
25%
30%
35%
Percentage of respondents who selected each option (N=24)


5. At what age was the affected individual diagnosed with GM1?
0-6 months
7-12 months
13-24 months
25-36 months
4-5 years
6-10 years
11-20 years
21-30 years
31-40 years
41-60 years
Unsure
8%
8%
28%
32%
8%
16%
0%
0%
0%
0%
0%
Response options
0%
5%
10%
15%
20%
25%
30%
35%
Percentage of respondents who selected each option (N=25)

Appendix 2: Meeting Agenda

Friday October 14th, 2022

10:00 - 10:05 am	Welcome from Cure GM1 Foundation
	Christine Waggoner, Founder & President
	Cure GM1 Foundation
10:05 - 10:10 am	Invited FDA Speaker
	Wilson Bryan, MD CBER, FDA
10:10 - 10:25 am	GM1 Gangliosidosis Disease Clinical Overview
	Cynthia Tifft, MD, PhD
	National Human Genome Research Institute
10:25 - 10:35 am	Introduction and Meeting Overview
	James Valentine, JD Hyman, Phelps, McNamara
10:35 - 10:40 am	Audience Demographic Polling
10:40am -12:30 pm	**Topic 1: Living with GM1 Gangliosidosis**
	Panel Discussion
	Audience and Remote Polling
	Moderated Audience Discussion
12:30 – 1:00 pm	Lunch Break
1:00 - 1:10 pm	GM1 Gangliosidosis Research and Treatment Landscape
	Jeanine Jarnes, PharmD University of Minnesota
1:10 - 2:45 pm	**Topic 2: Current and Future Treatments for GM1**
	Panel Discussion
	Audience and Remote Polling
	Moderated Audience Discussion
2:45 - 2:55 pm	Summary of the Day
	Larry Bauer, RN, MA Hyman, Phelps & McNamara
2:45- 3:00 pm	Closing Remarks from Cure GM1 Foundation
	Christine Waggoner, President & Founder Cure GM1 Foundation

Appendix 3: Meeting Discussion Questions

Session 1: Living with GM1: Symptoms and Daily Impacts

1. Of all the symptoms and health effects of GM1, which 1-3 symptoms have the most significant impact on your loved one's life?

2. How does GM1 affect your loved one on best and on worst days?

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

4. Are there specific activities that are important to your loved one that you cannot do at all or as fully as you would like because of GM1?

5. What do you fear the most as your loved one gets older? What worries you most about your loved one's condition?

Session 2: Current & Future Approaches to Treatment

1. What are you currently doing to manage your loved one's GM1 symptoms?

2. How well do these treatments address the most significant symptoms and health effects of GM1?

3. What are the most significant downsides to your loved one's current treatments and how do they affect daily life?

4. Short of a complete cure, what specific things would you look for in an ideal treatment for GM1? What factors would be important in deciding whether to use a new treatment?

Appendix 4: Meeting Participants

Session 1: Discussion starters

- Douglas, father of a 14-year-old girl living with Type 2B, juvenile GM1
- Abby, mother of a son living with Type 1, infantile GM1
- Bence, father of a two-year-old girl living with Type 1, infantile GM1
- Megan, mother of a five-year-old daughter living with Type 2A, late infantile GM1
- Kylie, mother of nine and six-year-old daughters living with Type 2B, juvenile GM1

Session 1: Zoom Panel

- Lindy, mother of a 14-year-old son living with Type 2A, late infantile GM1
- Jenny, mother of an eight-and-a-half-year-old daughter living with Type 2A, late infantile GM1
- Stephanie, mother of a one-and-a-half-year-old son living with Type 2A late infantile GM1
- Cindy, mother of a 34-year-old son living with an unusual form of GM1 with both juvenile and adult-onset characteristics
- Brittany, mother of a two-and-a-half-year-old son living with Type 2A, late infantile GM1

Session 1: Callers

- Matt, father of a five-year-old daughter living with Type 2A, late infantile GM1
- Ruth, mother of a 20-year-old daughter living with Type 2B, juvenile GM1
- Amy, grandmother and caregiver of a boy living with Type 2A, late infantile GM1
- Melinda, grandmother of a granddaughter living with Type 2A, late infantile GM1
- Tania, grandmother of a granddaughter with Type 1, infantile GM1, who passed away

Session 2: Discussion starters

- Ryan, parent of an eight-year-old daughter living with Type 2B, juvenile GM1
- Tom, father of an 18-year-old daughter living with Type 2B, juvenile GM1
- Rojan, mother of a five-year-old son living with Type 2A, late infantile GM1
- Ronnie & Rachael, parents of a 10-year-old son living with Type 1, infantile GM1
- Niclas, parent of three children living with Type 2A, late infantile GM1

Session 2: Zoom Panel

- Jessica, mother of a daughter with Type 1, infantile GM1, who has passed away
- David, father of an infant daughter living with Type 2A, late infantile GM1
- Marilee, mother of three children diagnosed with Type 2A, late infantile GM1, including two who passed away
- Maria, mother of 14 and six-year-old sons living with Type 2B, juvenile GM1
- Martha, grandmother of a grandson living with Type 2A, late infantile GM1

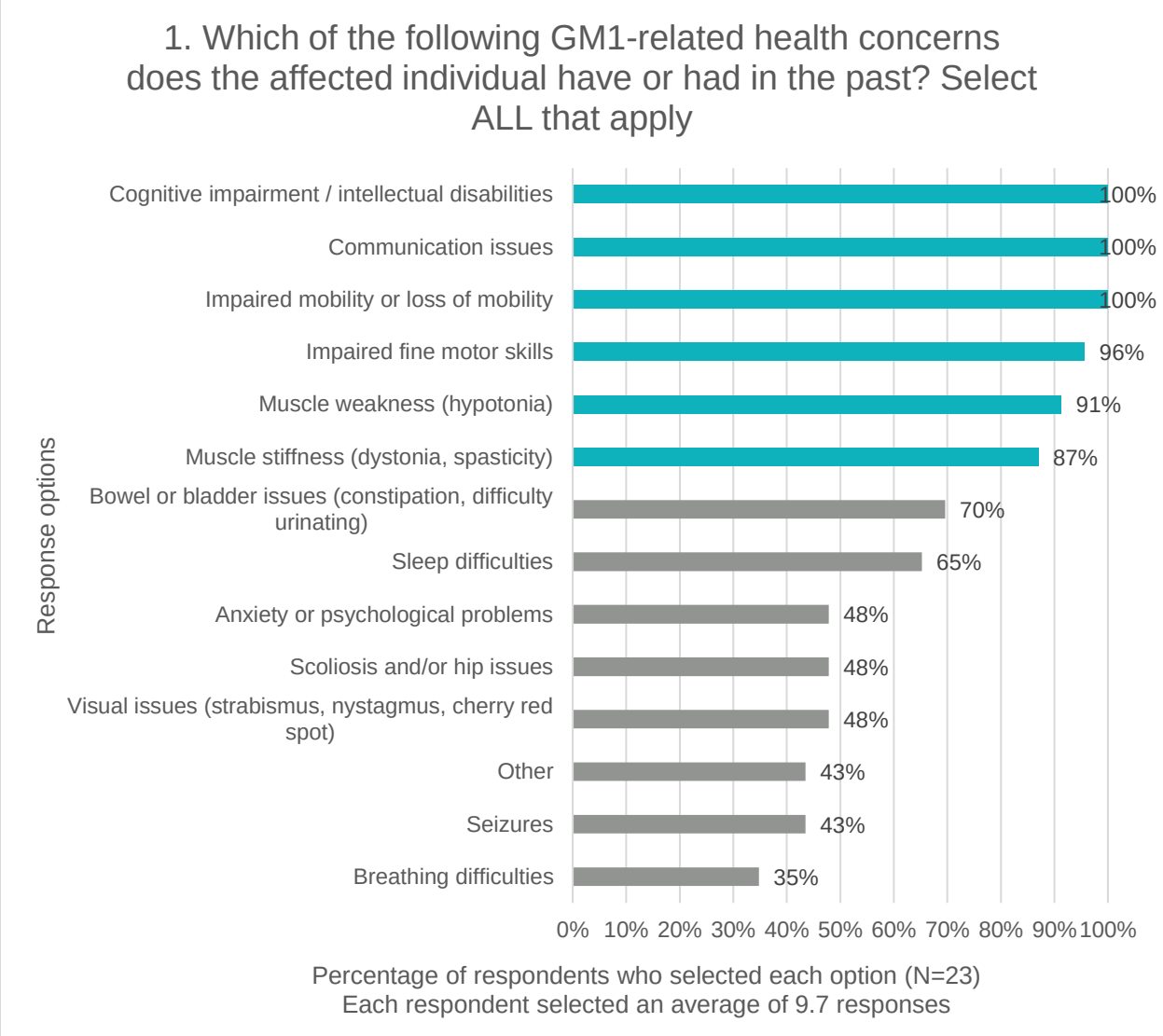
Session 2: Callers

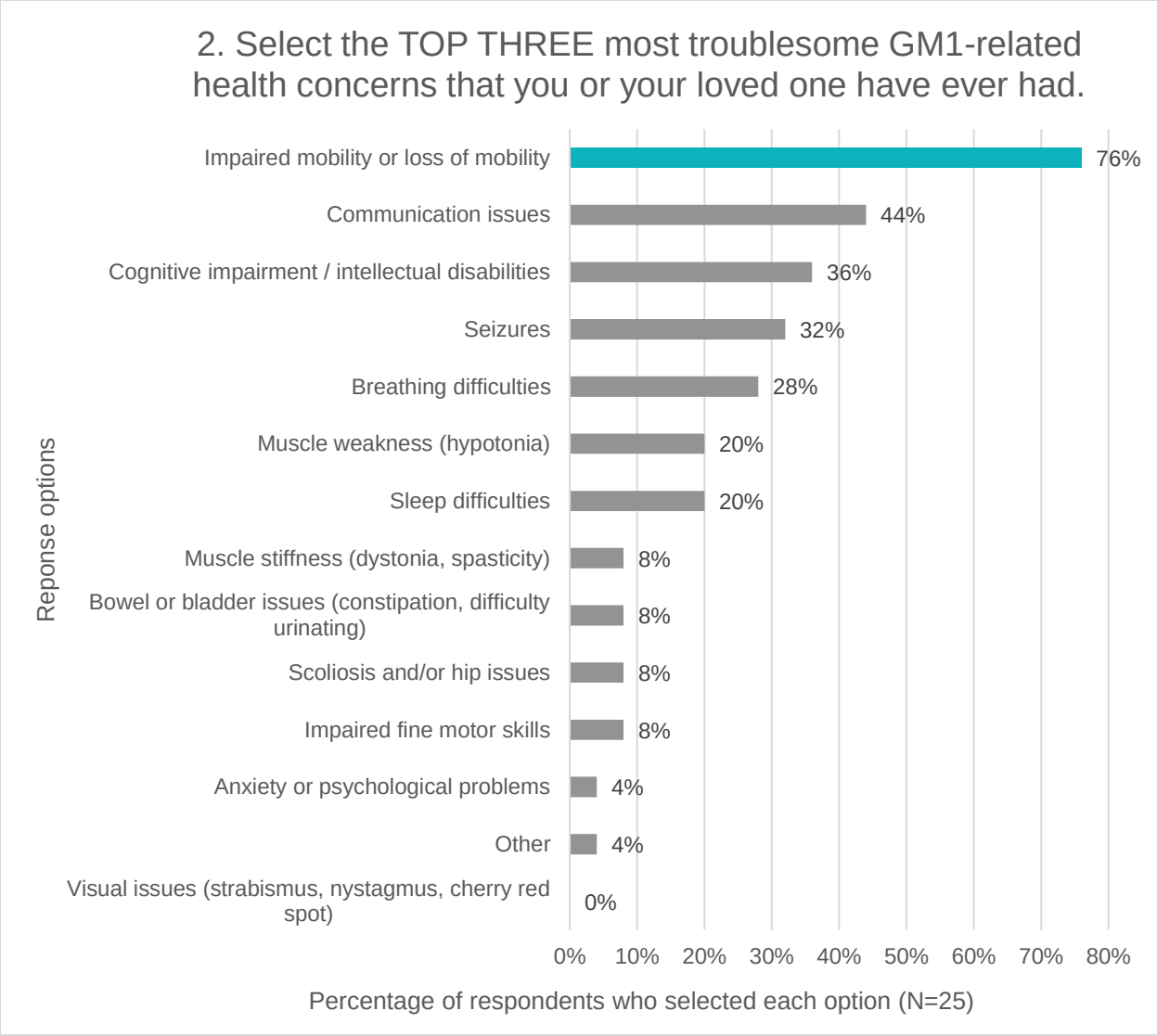
- Cindy, mother of a 34-year-old son living with an unusual form of GM1 with both juvenile and adult-onset characteristics

Appendix 5: Topic 1 Poll Results: Living with GM1 gangliosidosis

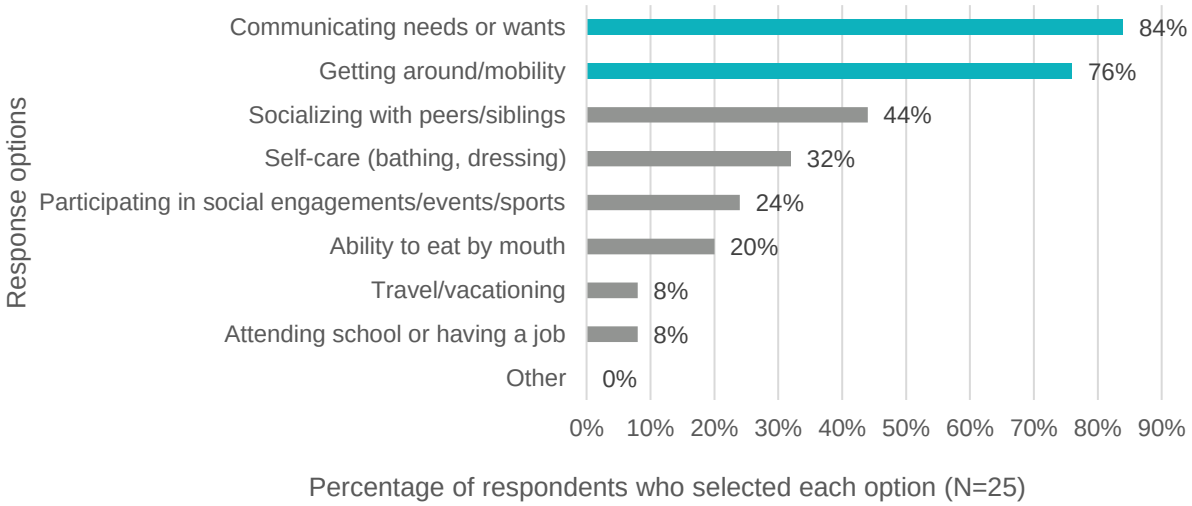
The graphs below include all meeting attendees who chose to participate in online voting. The number of parents and caregivers who responded to each polling question is shown below the X axis (N=x).

The responses for these polling questions are provided to present a snapshot of those who participated in the GM1 EL-PFDD meeting and is intended to complement the patient comments made during and after the meeting. The teal shading emphasizes top response option(s) selected for each poll question and were the options discussed most frequently during the meeting and in the online comments.

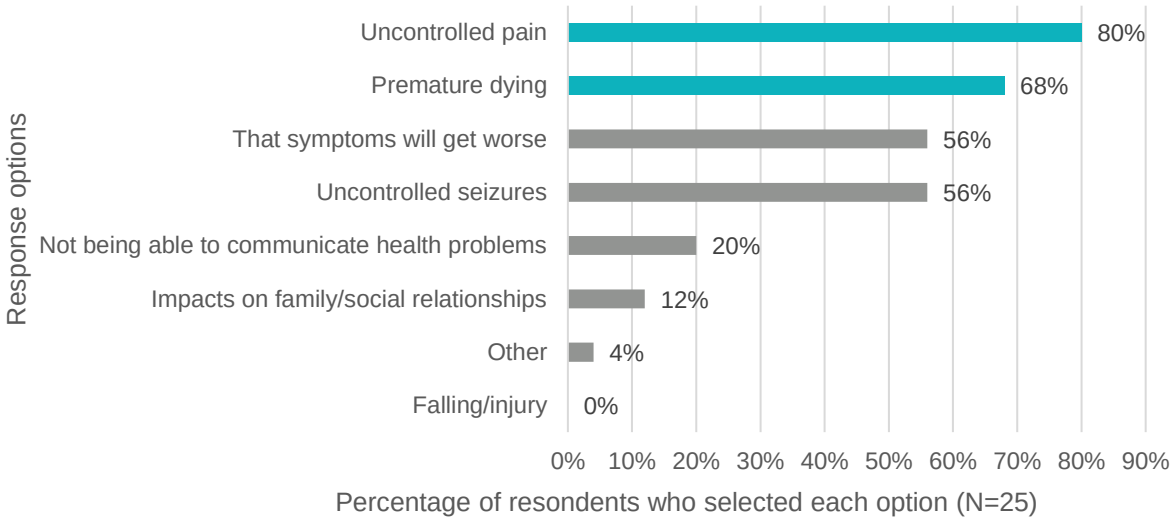



2. Select the TOP THREE most troublesome GM1-related health concerns that you or your loved one have ever had.
Reponse options
Impaired mobility or loss of mobility
76%
Communication issues
44%
Cognitive impairment / intellectual disabilities
36%
Seizures
32%
Breathing difficulties
28%
Muscle weakness (hypotonia)
20%
Sleep difficulties
20%
Muscle stiffness (dystonia, spasticity)
8%
Bowel or bladder issues (constipation, difficulty urinating)
8%
Scoliosis and/or hip issues
8%
Impaired fine motor skills
8%
Anxiety or psychological problems
4%
Other
4%
Visual issues (strabismus, nystagmus, cherry red spot)
0%
0%
10%
20%
30%
40%
50%
60%
70%
80%
Percentage of respondents who selected each option (N=25)

3. What specific activities of daily life ~~that~~ are important to you (or your loved one) that you/they are NOT able to do or struggle with due to GM1? Select TOP THREE



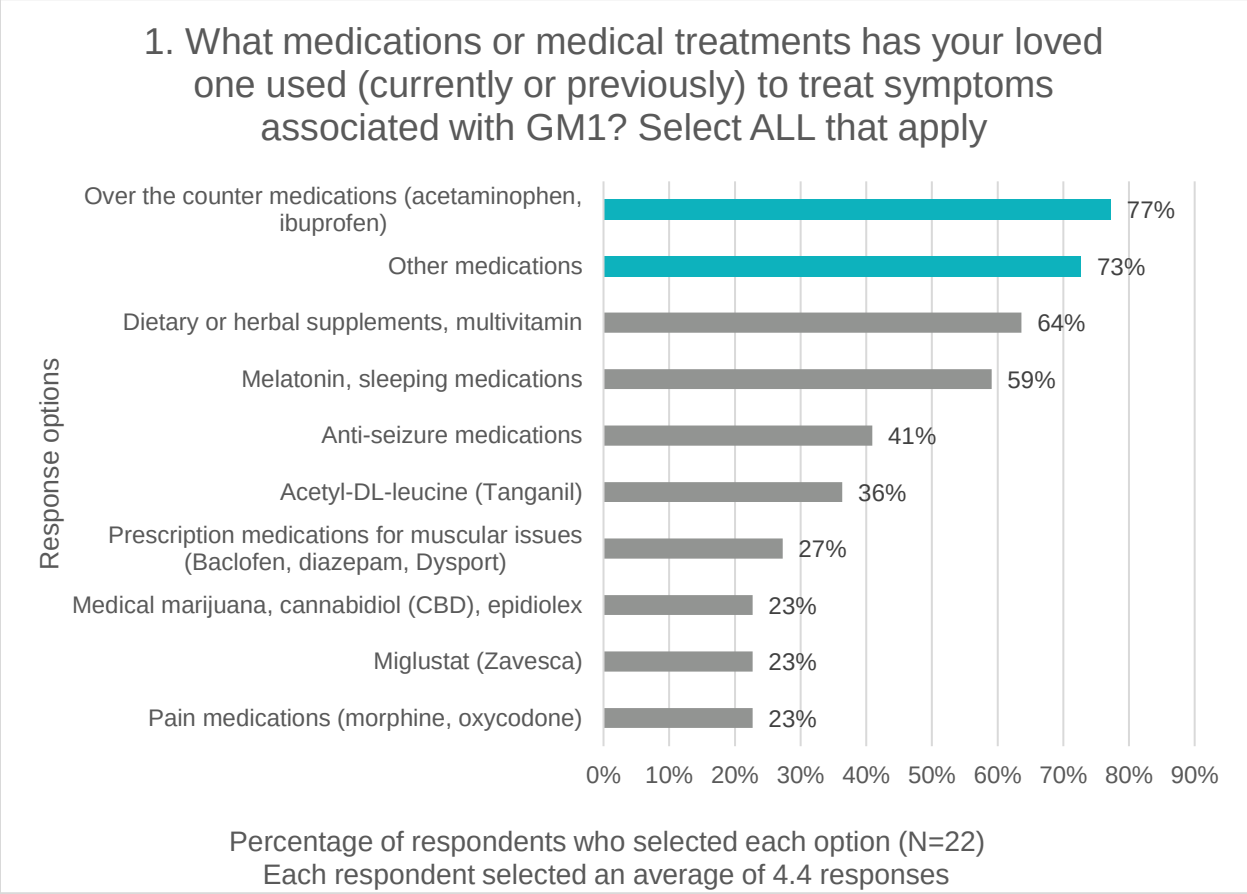
4. What worries you most about your loved one's condition in the future? Select TOP THREE

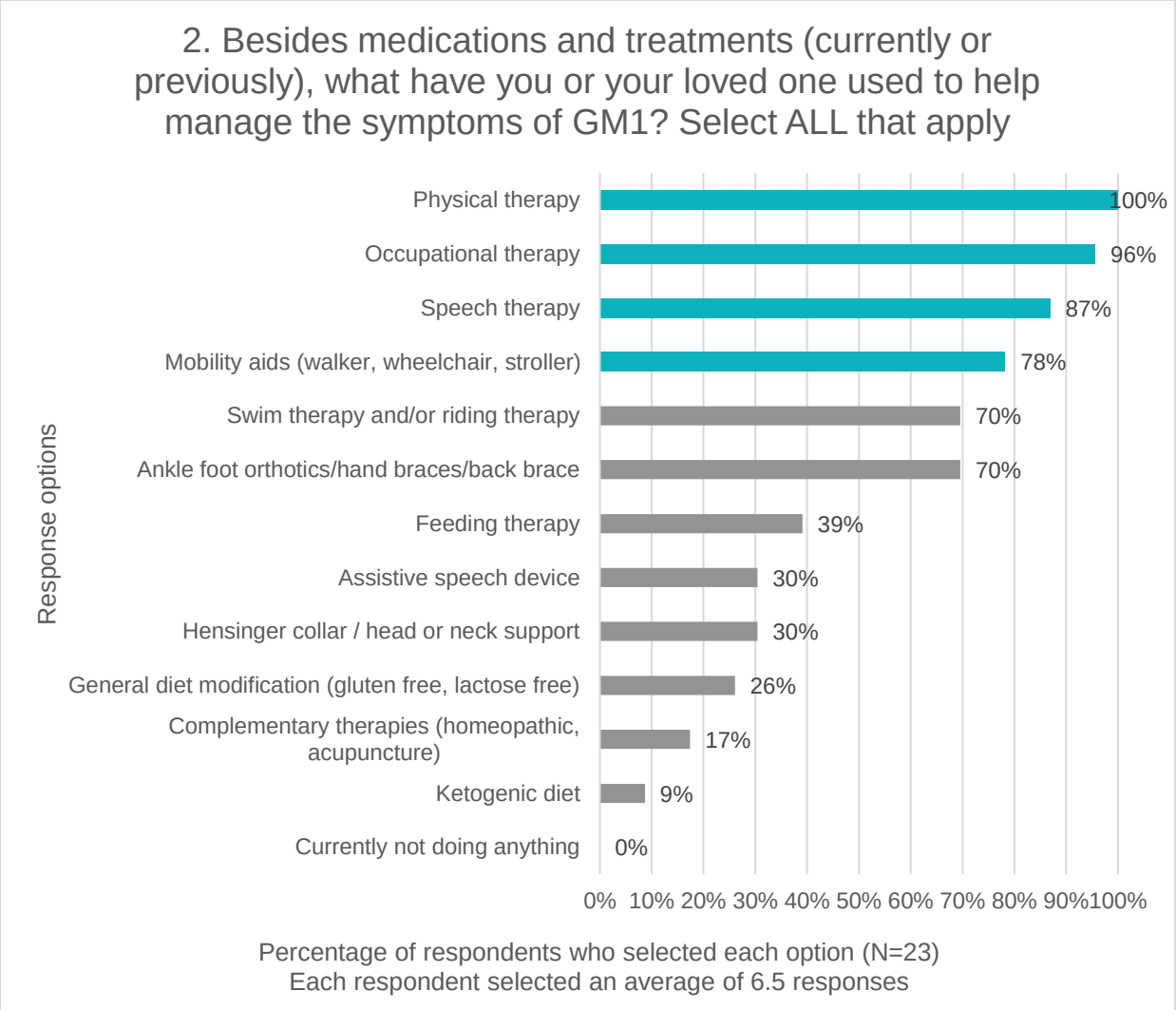


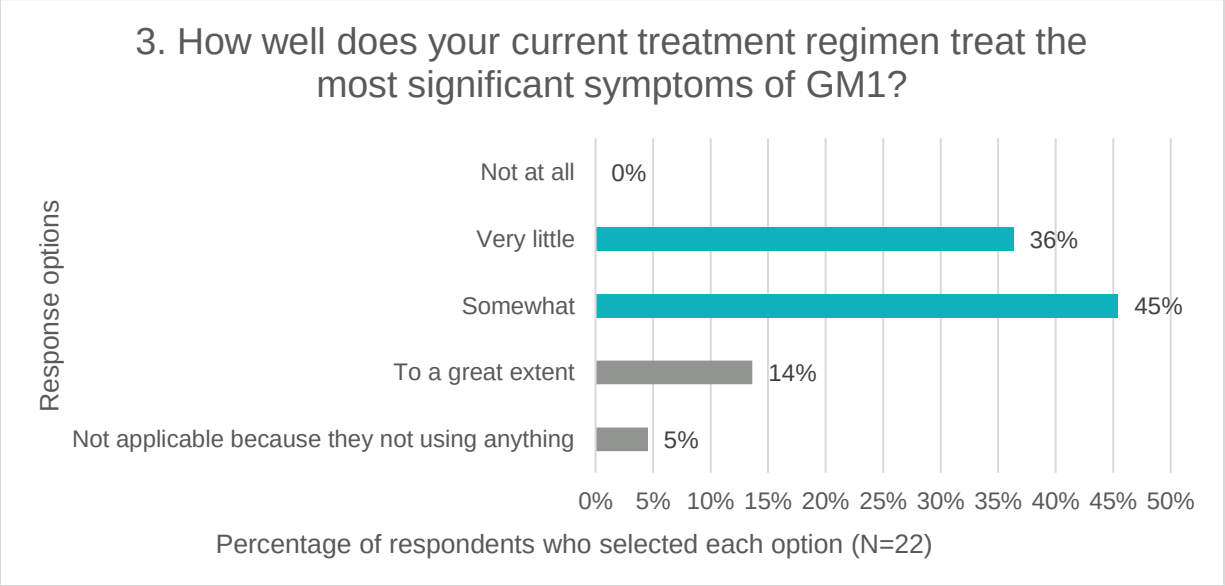
Appendix 6: Topic 2 Poll Results: Current and Future Treatments for GM1

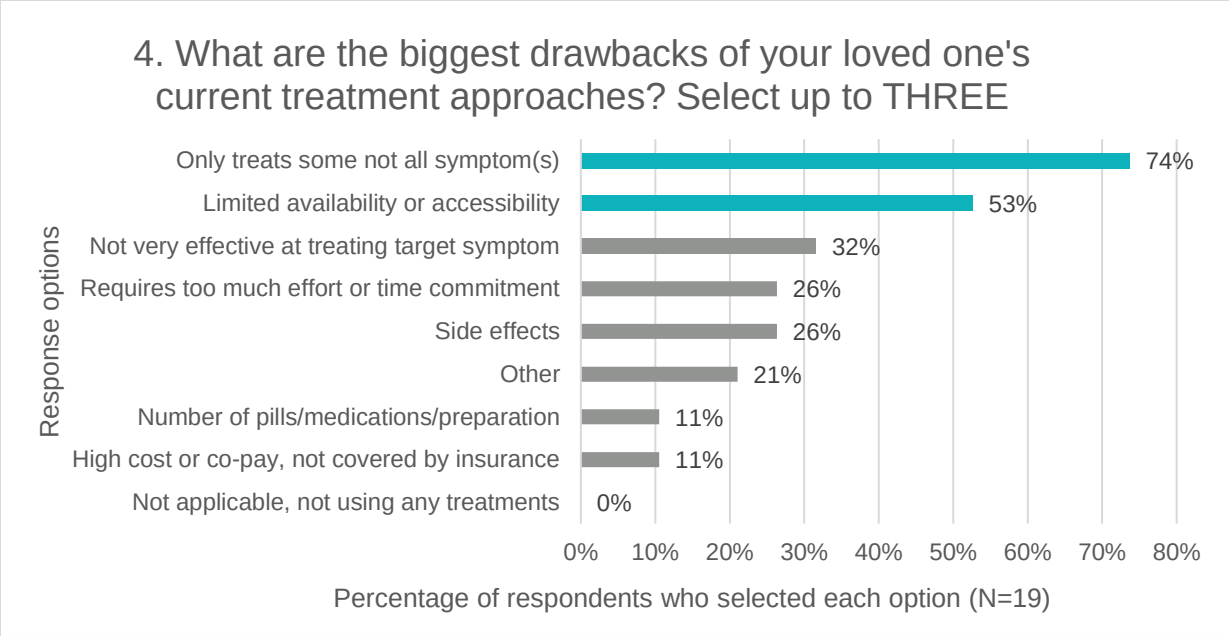
The graphs below include all meeting attendees who chose to participate in online voting. The number of parents and caregivers who responded to each polling question is shown below the X axis (N=x).

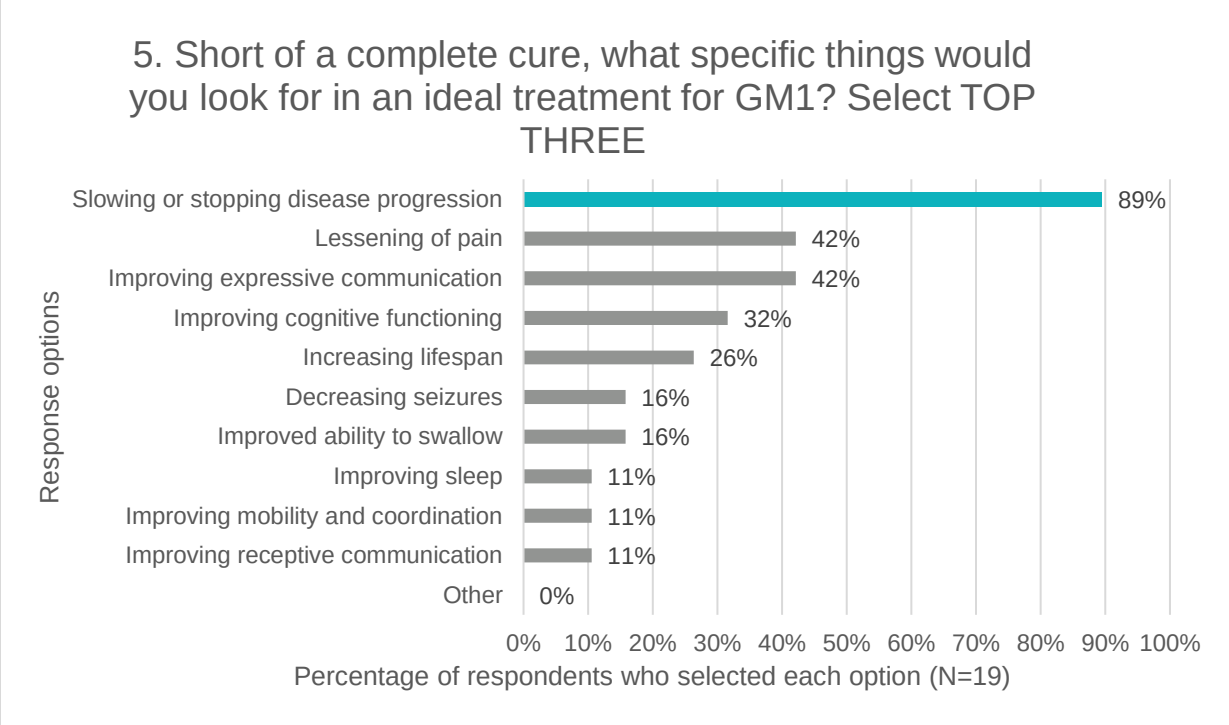
The responses for these polling questions are provided to present a snapshot of those who participated in the GM1 EL-PFDD meeting and is intended to complement the patient comments made during and after the meeting. The teal shading emphasizes top response option(s) selected for each poll question and were the options discussed most frequently during the meeting and in the online comments.




2. Besides medications and treatments (currently or previously), what have you or your loved one used to help manage the symptoms of GM1? Select ALL that apply
Response options
Physical therapy 100%
Occupational therapy 96%
Speech therapy 87%
Mobility aids (walker, wheelchair, stroller) 78%
Swim therapy and/or riding therapy 70%
Ankle foot orthotics/hand braces/back brace 70%
Feeding therapy 39%
Assistive speech device 30%
Hensinger collar / head or neck support 30%
General diet modification (gluten free, lactose free) 26%
Complementary therapies (homeopathic, acupuncture) 17%
Ketogenic diet 9%
Currently not doing anything 0%
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Percentage of respondents who selected each option (N=23)
Each respondent selected an average of 6.5 responses


3. How well does your current treatment regimen treat the most significant symptoms of GM1?
Response options
Not at all 0%
Very little 36%
Somewhat 45%
To a great extent 14%
Not applicable because they not using anything 5%
0% 5% 10% 15% 20% 25% 30% 35% 40% 45% 50%
Percentage of respondents who selected each option (N=22)


4. What are the biggest drawbacks of your loved one's current treatment approaches? Select up to THREE
Response options
Only treats some not all symptom(s)
Limited availability or accessibility
Not very effective at treating target symptom
Requires too much effort or time commitment
Side effects
Other
Number of pills/medications/preparation
High cost or co-pay, not covered by insurance
Not applicable, not using any treatments
74%
53%
32%
26%
26%
21%
11%
11%
0%
0% 10% 20% 30% 40% 50% 60% 70% 80%
Percentage of respondents who selected each option (N=19)


5. Short of a complete cure, what specific things would you look for in an ideal treatment for GM1? Select TOP THREE
Response options
Slowing or stopping disease progression
Lessening of pain
Improving expressive communication
Improving cognitive functioning
Increasing lifespan
Decreasing seizures
Improved ability to swallow
Improving sleep
Improving mobility and coordination
Improving receptive communication
Other
89%
42%
42%
32%
26%
16%
16%
11%
11%
11%
0%
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Percentage of respondents who selected each option (N=19)

Appendix 7: Caregiver Study of most important symptoms to treat for GM1 gangliosidosis

A caregiver study was conducted to describe the unmet treatment needs of children with GM1 and identify priority symptoms to treat, as characterized by parents and caregivers of children with GM1 gangliosidosis. The objective of this original research on GM1 was to inform patient-focused drug development by characterizing meaningful and prioritized symptom targets, which will also inform the identification of clinical trial outcome measures.

The manuscript has been published by the American Journal of Medical Genetics.[4] The abstract is presented below.

GM1-gangliosidosis: The caregivers' assessments of symptom impact and most important symptoms to treat

Bingaman, A, et al.

Abstract

GM1-gangliosidosis, or GM1, is a rare neurodegenerative disorder that leads to early mortality and causes progressive decline of physical skills and cerebral functioning. No approved treatment for GM1 exists. In this study—the first to explore the priorities of parents of pediatric GM1 patients—we address a crucial gap by characterizing the most critical symptoms to treat. Our two-phase, mixed-methods approach began with focus groups, followed by interviews with a distinct set of parents. The interview phase included a prioritization activity that used best-worst scaling. Quantitative data were analyzed descriptively. Qualitative data were analyzed using thematic analysis and rapid analysis process. Parents prioritized the symptoms they believed would increase their child's lifespan and improve their quality of life (QoL), which included symptoms focused on communicating wants/needs, preventing pain/discomfort, getting around and moving one's body, and enhancing eating/feeding. Although lifespan was highly valued, almost all parents would not desire a longer life without acceptable child QoL. Overall, parents indicated high caregiver burden and progressive reduction in QoL for children with GM1. This novel study of caregiver priorities identified important symptoms for patient-focused drug development in the context of high disease impact and unmet treatment needs.

[4] Bingaman A, Waggoner C, Andrews SM, et al: GM1-gangliosidosis: The caregivers' assessments of symptom impact and most important symptoms to treat. American Journal of Medical Genetics Part A 191:408-423, 2023

Appendix 8: Additional parent and caregiver comments submitted online

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 GM1 EL-PFDD meeting. Submitted comments were first sorted by the order in which they were submitted and then by the respondent. Respondents are identified by their first name only. Selected comments are included in the main body of the *Voice of the Patient* report.

Comments were edited only slightly for spelling and punctuation, and comments perceived to be disrespectful to individuals, companies or organizations were not included. The names of all children living with GM1 were removed for privacy reasons.

Christina, grandmother of a kindergarten-aged boy living with GM1

I'm Christina, [our grandson's] grandmother.

Our [grandson] is a fighter and he is doing well so far.

He has many therapies every week such as ergotherapy, speech therapy, physiotherapy, riding therapy, he goes to a farm where he deals with animals therapeutically. He likes going to the animals best. He loves the sheep, cows, chickens, cats and dogs. They give him a lot and have a positive effect on his health.

Last June he received a triple dose of gene therapy as part of the SIO study.

When [our grandson] is having a good day, he feels good, then he is very concentrated, he runs better and longer distances, his hands are not cramped and his speech is clearer, he is more confident and his balance is very good, his fine motor skills are better developed.

All this is different on less good days. He can only concentrate less well, his hands are cramped, his speech is more slurred, he cannot walk very long distances.

On the 27th of August, [our grandson] becomes a schoolchild. He is full of anticipation and very excited for the big day. He will be supported at school by a school companion who will support him if he needs help. Christina, grandmother of a kindergarten-aged boy living with GM1

Ronnie, father of a 10-month-old infant son living with Type 1, infantile GM1

The most significant symptom which is impacting our life is the fact that we see our son regressing and knowing what he will go through, for him we believe it is his low muscle tone as he is not able to hold himself and the issues with his breathing.

He smiles whilst playing and holds small toys in his hands when he is on his best days which at the moment are still quite frequent, and automatically that would be a good day for us too. There are some days in which he is sleepy and seems tired and not seeing him able to move obviously means that it saddens us too.

Obviously being almost 10 months old at the moment it would be expected that he is more active and he would be able to interact with us more but unfortunately due to the condition he is not able to do that, thus it restricts us from doing most activities that other children at his age do with him.

Since he has been regressing lately, he is having issues with [oxygen] desaturations, thus it has restricted him to being dependant on a high flow machine 24/7.

Nolan, parent of a child with Type 1 infantile GM1, who passed away

Comment 1: Of all the symptoms the most significant to my son was the swelling. By the end he was so swollen he could barely move and couldn't even smile anymore.

He couldn't walk, lost his ability to sit up, and then his eye-sight along with being able to move his arms and smile. So he wasn't able to play anymore or even watch tv.

His ability to cope, he always smiled. From the time he was born, when he was in the hospital and it was his birthday. All the way until he was so swollen he couldn't smile anymore. And he could make sounds to let you know he wanted to smile and was frustrated that he couldn't.

Comment 2: With gene therapy is there non-invasive options?

My son had breathing issues from the beginning and couldn't even go under to get his pic line changed sides. So invasive surgeries wouldn't be a option.

Comment 3: NA - He passed away

Joslane parent of child with GM1

Quando temos o diagnostico o mundo desmorona sobre nossa cabeça. Temos medo da perda... E do novo... Mas com por nossos filhoa amados temos que levantar e lutar... Lutamos até o último suspiro de nossa pequena [filha's] e mesmo sabendo que um dia a morte viria... Lutamos pelo seu bem estar geral, pelo conforto dela e fizemos tudo que estava ao nosso alcançe para ela ter qualidade de vida. Esperamos que a terapia genetica venha e torcemos que de certo e salvem muitas vidas. Doença rara e muito cruel essa GM 1.

Joslane, parent of daughter living with GM1 (translated from Portuguese)

When we have the diagnosis, the world collapses on our head. We are afraid of loss... And of the new... But with our beloved children we have to stand up and fight... We fight until our little [daughter's] last breath and even though we know that one day death would come... for her general well-being, for her comfort and we did everything in our power for her to have quality of life.

We hope that gene therapy will come and we hope that it will work and save many lives. Rare and very cruel disease this GM1.

María José, mother of a 20-year-old daughter living with Type 3, adult onset GM1

My name is María José and I am the mother of [our daughter], 20 years old, affected by GM1 type 3.

Since we got [our daughter's] diagnosis six years ago after several misdiagnoses, our lives changed completely living as [our daughter's] gradually gets worse and loses her abilities.

The impact of the diagnosis was brutal, the word degeneration still haunts my brain.

The dystonia that [our daughter] suffers from is generalized, it prevents her from speaking fluently and she suffers from pain in the neck, shoulder and right arm, apart from other

symptoms, she is aware of how GM1 is taking over her body and she can do fewer and fewer things, she still walks but It is agony to think how much time is left, how much time is left to listen to that thread of voice, or how much time is left to use your hands.

When it has good days it crosses our minds that GM1 could stop at that point and not move forward even though we never lower our guard, but when it has bad days the feeling is very dark, you feel powerless and look for a thousand alternatives to alleviate that bad day.

[Our daughter], apart from suffering several symptoms, suffers from the indifference of society, seeing that she cannot keep up with others, especially with young people her age, she suffers from the loneliness of friends and that leads her to suffer from depression as she sees each other more and more. more limited, not being able to speak fluently plunges her into depression and she isolates herself more and more, she feels that she never fits in anywhere."

I see how the ones around her advance and she gets stuck.

She managed to graduate from high school and stopped studying because of GM1, she got her driver's license, and she had the feeling of driving a car, but she barely drives anymore because of the insecurity caused by GM1.

We do not have a clear future for [our daughter], it is very painful to think what will happen when time passes, what state will [our daughter] will be in, what will become of her.

The milestone expectations about [our daughter] are disappearing as time goes by.

As an adult, she understands more that she has to take care of her body, although she is burned out from being in therapy for so many years and sometimes she leaves because she is mentally exhausted, although after a while she reconsiders and resumes her therapies.

I dream of a cure for [our daughter] and that she will have time to lead a normal life. May she reach all those affected GM1 especially the boys and girls who suffer from it.

Arlene, mother of a 33-year-old son living with Type 2 GM1

I thought Botox helped my son, age 33 with GM1 Type 2

He was receiving Botox every 3 months at U of M for over 2 years. Hasn't been for Botox treatment for 2 years due to Covid. I see no difference.

Amy, grandmother and caregiver of a grandson living with Type 2A, late infantile GM1

Comment 1: At this time, the most significant symptoms are the hypotonia, and loss of speech, and now the possibility of seizures that we are in the process of maybe getting diagnosed.

Comment 2: Best and worst days.

Best. Days where [my grandson] has lots of energy, eats good, and walks with walker and just keeps going all day with no breakdowns. *[My grandson] is always a happy boy, his smile lights up our day.

Worst. No energy - just crawling wears him out, you can tell he's in pain and takes multiple naps, and the days when he is around his cousins and he just wants to play with them and can't.

Best. [My grandson] is happy, eating great, doing awesome during his therapies then going to the pool and swimming everywhere with his floaties on and just happy and playing with his cousins and friends.

Worst. [My grandson] has no energy, wants to be carried everywhere still smiling and happy but not as happy as his normal. He won't participate in his therapy sessions, you can tell he's in pain and just wants to sleep.

Pahtondra, mother of son with GM1

Comment 1: 1. No head control; 2. Respiratory issues; 3. Never being able sit up

Comment 2: Best days are when [my son] was able to smile and still able to hold fingers and make different noises with his mouth.

Worst days were going in and out of the hospital for respiratory issues and watching him have trouble breathing.

Comment 3: I would have loved for [my son] to have head control it would have made his life a little bit easier. But he never knew any different, so he didn't know what he was missing.

Maria, mother of a son living with GM1

Comment 1: Of all the symptoms of GM1, the ones that have had the most impact on my child's life are: the loss of his ability to communicate effectively as most of his speech is not understandable anymore; the loss of his ability to do things for himself such as dressing, toileting, and entertaining himself; and the regression in his motor abilities causing him to have difficulty walking long distances, navigating rough terrain and stairs, and causing him to no longer enjoy playgrounds.

Comment 2: My son was always a very happy and cooperative little boy. As he started to regress from GM1 he became fussier and less cooperative and over time as the disease has progressed and his ability to reason and process information has decreased, he has become more and more fussy. We have found a medication to help with this and he is overall much happier but the disease has definitely stolen his carefree and bubbly disposition of his early years.

Deborah, mother of sons with GM1, who has passed away

Symptoms that have significantly affected our family while my boys were alive was not being able to communicate with me when they were in pain or what they needed, their lack of body control that continually got them hurt, and the seizures that caused them to be out of it afterwards or the fear of a seizure in their sleep and them passing in their sleep.

Victoria, mother of an adult daughter living with GM1

Among the symptoms we encountered are 1-loss of speech, 2-reckless behavior towards younger sister (may pull hair), 3- misunderstanding of danger. How this disease affected us: constant fear of not being able to make time, when [our daughter] pulls something in her mouth or walks quickly. The worst thing is that she can't talk about the pain and show where it hurts.

She turned into a child at the age of 15. The warmest emotions are when she hugs you for a kiss and remembers familiar songs from childhood with an emotional cry.

Debra, parent of a 19-year-old son living with Type 2B, juvenile GM1

Comment 1: The most significant impacts have been [our son's] gradual loss of cognitive and physical functions. He has the mental capacity of a 1 to 2-year-old. He is incontinent and requires a wheelchair. The avascular necrosis in in his hips cause him great pain during transitions, and he is currently being evaluated for a hip replacement.

Comment 2: Hi, I'm Debra, mother of a 19-year-old [son], who has GM-1 type 2. He's in a wheelchair, and is profoundly cognitively impaired. We've found travel by plane too difficult for the same reasons Cindy mentioned, but have continued to travel with him by RV. Obviously, as Cindy noted, we can't do everything we want to do together, but there are quite a few activities we can do, and [our son] really seems to enjoy traveling. Unfortunately, right now gas prices are through the roof, making RV travel less attractive for a lot of people, but it has been a viable alternative for us in the past few years.

Katie, mother of a child living with GM1

Comment 1: Inability to move, highly susceptible to illness, not able to verbally communicate were symptoms that affected us the most. Due to these symptoms, it was very hard to participate in everyday activities such as school, social gatherings, and travel.

Comment 2: Our best days were calm quiet and comfortably laying in bed or couch snuggling but still busy with feeding and med schedule, suctioning, frequent position changes.

Our worst days were difficulty breathing, not being able to tolerate feeds, many hard seizures, storming, restlessness from discomfort, fear of it being our last days but also hoping the pain would end.

Manuel, father of a son with Type 1 infantile GM1 who passed away

Of all the symptoms of GM1, which 1-3 symptoms have the most significant impact on you or your loved one's life?

The most significant impact on [our son] in his initial months was the ability to maintain a steady position. During the course of time he had problems with breathing normally and swallowing.

How does GM1 affect you or your loved one on best and on worst days? Describe your best days and your worst days.

Although knowing [our son]'s condition and all the consequences the best days were those which we lived together doing memories...vacations and stays at home. Worst days were those days spent in hospital especially the last month seeing his condition deteriorating.

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 GM1?

The inability to stand steady and to live a normal live which are very common in GM1 Type 1 prevent from doing most activities

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

Unfortunately not. The condition progressed and managed to win. As time passed by the symptoms increased.

Diana, friend of a family with a child living with Type 2A, late infantile GM1

I have watched dear friends walk through GM1 for several years now. The slow degradation in [our loved one's] abilities has been heartbreaking to watch, but more than that is the defeat and questioning that I see her parents live with day in and day out. They question what they did to harm their daughter when crying fits start, often running into the 24-36 hours in duration. She is non-verbal and cannot articulate her needs effectively, which leaves family constantly trying new things to sooth, chasing recovery meds that leave her not herself, running to the ER for help that they are not equipped to give with this rare disease, and simply hopeless for the quality-of-life that she deserves. Over time this has left parents and siblings in a state of deep PTSD and longing for joy and more and more elusive 'good days.'

While we know that there is nothing these parents wouldn't do for their children, often suffering through nights of crying endlessly, becoming essentially trained nursing staff without the degree, and loving her deeply. This and other rare diseases leave caregivers alone and struggling to cope as they have little support from the medical community, no cure to hang hopes on and in desperate need to soothe and comfort their daughters and sons in the later stages of this disease. My hope is that awareness and energy can be put into caregiver support AND a cure.

São, mother of a 14-year-old daughter living with Type 2B, juvenile GM1

Comment 1: [Our daughter] is 14 years old, she is from Portugal and has GM1 gangliosidosis, type 2. She was born by caesarean section, developed well in early childhood but started symptoms from the age of 7. It has already regressed a lot, the motor part, cognitive but mainly in speech. Is there a genetic test for children of this age? We urgently need the FDA to help children and authorize the drugs. Thanks

Comment 2: We are from Portugal. I'm [our daughter's] mother who has GM1 Gangliosidosis, type II (juvenile). Symptoms started at age 7. Now 14 years old, she has regressed a lot. I am part of the DOCE Association in Portugal and we have more children with this type of rare disease. We really want to treat our children. Thank you

Comment 3: [Our daughter] developed very well in early childhood and as a baby. It wasn't until age 7 that she started to sit and move differently on the floor. She fell a lot. We thought it could be some sort of inner ear problem. At age 8, she began to stutter and speak badly. We went to the doctors. We did tests until the neuro-pediatrician asked for genetic tests. At age 9, we knew the diagnosis, GM1 gangliosidosis, type II. It was as if a bomb had gone off. She is now 14 years old and is a happy child with a beautiful smile.

She attends a regular school but with special education. She has many difficulties, but we try to encourage and help her so that she doesn't lose her abilities. He does hydrotherapy, hippotherapy, speech therapy and physiotherapy, because he has scoliosis. I am very anxious waiting for possible treatments or genetic tests for her because she is regressing. She is my life and my princess. Thank you all.

Karen, mother of a daughter living with Type 3, adult-onset GM1

Q1

a - loss of speech

b - loss of mobility

c - 24/7 pain

Q2

Best day

Able to get [our daughter] up and ready to face the day

Worst day

Unable to function in every aspect of daily life

Q3

Unable to access all activities without 100% support

Q4

Went from normal 16-year-old to being unable to walk, talk and be 100% dependant on me in less than 10 years

Melinda, grandmother of a granddaughter living with Type 2A, late infantile GM1

Comment 1: With regard to #3, the answer is everything. My grandchild can't walk, talk, hold up her head, sit on her own, eat (she's on a feeding tube), move her bowels without external assistance, interact with those around her, and her symptoms increase and worsen at an alarming rate. Time is the enemy with GM1. It deprives its victims of abilities to function in every way.

Comment 2: Clinical trials for GM1 have been including only children who have mild symptoms or are pre-symptomatic. There are many parents of children with a more advanced stage of GM1 who would like the opportunity of trying some kind of treatment. They realize the risks, but the alternative is simply watching their children regress & waiting for them to die. Since GM1 is universally fatal, giving them even a long shot of a chance to improve their quality of life should be available.

Ruth, mother of a 20-year-old daughter living with Type 2B, juvenile GM1

Comment 1: I'm the mother of a beautiful 20-year-old girl. She is a happy and positive girl and teaches me to be strong and happy. She, like all those children in the world, deserve a chance to have a better life, like all human beings. Please approve the meds that these wonderful scientist's have developed for our children.

Comment 2: [Our daughter] has type 2 juvenile. Just as explained by Dr. Tifft, she was not diagnosed until she was 10. She developed like a normal child until 3. Then, we thought she had a speech impediment, but then she started falling and showing signs of mental retardation, or that's what doctors said she had. She was able to walk and run, she loved swimming and traveling, animals, dolls and princess movies. Loved wearing fancy clothes, she was funny and had and still has so much personality! She can't walk or talk now. We feed her, change her diapers, give her showers and do everything for her. She has a gait trainer and we take her for

walks. We take her to the pool, but it takes a lot of work on our part to get her ready, shower her, etc. it's also harder and harder for her to chew. We still travel, but it's getting harder to transport her. She has had some major surgeries; her hip was replaced and her gall bladder and left ovary was removed. What was more difficult was to see her in pain and not knowing what she was going through and she couldn't tell me. Her doctors didn't help. I found Dr. Tifft and she told me to take her to an orthopedist because she had avascular necrosis of the femoral head. She was in so much pain, limping and we didn't know what was happening! I feel so bad letting this happen for so many years to the point her whole femur head was disintegrated! Same thing with her gall bladder. She started throwing up in pain and couldn't tell me. The doctors did the surgery hoping that would take care of her vomiting and thankfully it did. We try to make her comfortable and move her to her bed, sofa, chair, car, gait trainer, etc. I just wish her body was not like this. I wish I could at least arrest the disease to avoid the horrible conditions that arise as the condition progresses. Please help us parents, help our children and adults to give them some relief!

James, best friend of a parent caring for a 14-year-old son living with Type 2A, late infantile GM1

Thank you for holding this meeting. I have watched my best friend care for her son. I know that any help this meeting can provide would impact her and her son's life more than anyone can imagine.

Jeanine

What should people answer if the child has passed away?

Honey, aunt of a niece living with Type 2A, late infantile GM1

Comment 1: [My niece] clearly enjoys interacting with people most of all, but she cannot ask for attention or interact with her sibling, peers, and family without the other individual taking the initiative to interact with her. The older she gets, the less likely people outside of her immediate family and caregivers are to take that initiative. Peer interactions are certainly missing from her life most days. Even her interactions with her brother and cousins are often cut short because they can run and play and she cannot follow.

Comment 2: I would say treatment regimen helps somewhat because we are fighting a losing battle. We certainly need all of the equipment. We definitely use physical therapy, orthotic braces, Baclofen, and botox injections to help with muscle tightness. The medications help with keeping her bowels moving, combating motion sickness and excess drool (which she often aspirates due to loss of swallow reflex), and assisting with sleep. But every time we get one thing under control, something else develops.

Ashley, sister-in-law of a parent caring for a 14-year-old son child living with Type 2A, late infantile GM1

I am Lindy's sister-in-law. As Lindy has mentioned, [our loved one] hit his milestones young, and the disease caused regression. Watching Lindy take care of [our loved one] is amazing. She is the best caregiver. She gets [our loved one] out and about, however, it is not an easy task. Its packing him up, loading the vehicle with his medical equipment, accommodating his items for comfort because of his joint pain. Not everywhere is wheel-chair assessable either which causes issues. I have seen [our loved one] go through so much in his short life that no child

should ever have to go through. This disease is completely debilitating not only for the children but for the parents as well. When the children can't sleep/ neither can the parents and the parents still need to stay strong to continue the care around the clock.

Heather, friend of a caregiver

Loss of motor control and ability to speak

Loved one/parents feel desperate, hopeless, depressed and devastated

Cannot communicate with their child, play with child and won't watch him grow up

It waivers day to day. In the beginning it was devastating, a trial gave hope, then they weren't selected and back to devastation, they are currently in fight mode but have bad days and feel desperate.

Stephanie, mother of a son living with GM1

My son received gene therapy through Passage Bio 2.5 months ago and I already know it has given him more years of quality life than he would have had without treatment. Before the treatment, he was on a dramatic decline, rapidly losing skills and worsening quality of life. Since treatment, regression stopped entirely and he has been able to regain skills like taking steps, eating solids, and increased vocabulary. Even if it doesn't cure him, I would absolutely do this treatment again if given the chance. I wish it was already approved for other families as it has truly given us a new lease on life.

Cindy, parent of a son living with GM1

Please let the FDA know that we started taking miglustat 5 days after it was Fast Track approved by the FDA. It has improved things for our son even though it hasn't worked for others. Thank you FDA for fast-tracking drugs that we desperately need.

Linda, friend of a parent with a son living with GM1

Thank you so much for sharing your experiences, this session has been incredibly moving for me. I have a friend whose son has GM1.

Thinking of the impact that GM1 has on families, has there been a financial impact for families? Do families have any support for procuring the adaptations and therapies that are needed by patients living with GM1? If you do get some support, how can others help improve the situation to a place where you get the support you want/need?

Jenny, mother of a child living with GM1

Some of the treatments for one symptom exacerbate other symptoms. For example, Scopolamine used for motion sickness and to reduce drooling, exacerbates my child's constipation.