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

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Abstract

GM1-gangliosidosis (GM1) is a rare neurodegenerative disorder leading to early mortality and causing progressive decline of physical skills and cerebral functioning. No approved treatment for GM1 exists. In this study—the first to explore priorities of parents of subjects with pediatric onset forms of GM1—we address a crucial gap by characterizing symptoms most critical to caregivers of children with GM1 to treat. Our two-part, mixed-methods approach began with focus groups, followed by interviews with a distinct set of parents. Interviews 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 perceived quality of life (QoL); these 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 lifespan without acceptable child QoL. Parents indicated high caregiver burden and progressive reduction in QoL for children with GM1. This novel study of caregiver priorities identified important symptoms for endpoints' selection in patient-focused drug development in the context of high disease impact and unmet treatment needs.

KEYWORDS
burden, caregivers, GM1, patient-focused drug development, treatment priorities

1 | INTRODUCTION

GM1-gangliosidosis (GM1) is a progressive disorder with a prevalence estimate of 1 in 100,000–300,000 worldwide (Suzuki et al., 2014). The neurodegenerative genetic disorder involves developmental delay and regression of both physical skills and cerebral functioning and results in early death (Nicoli et al., 2021; Regier et al., 2016). The pediatric forms of GM1 are classified into subtypes based upon age at which the child first shows neurological symptoms that strongly indicate an abnormality in the child's development (Lang et al., 2020; Regier et al., 2016):

1. Early infantile GM1 (Type 1): Onset of symptoms by 12 months of age.

R. Vakili is the parent of child with GM1.

2. Late infantile GM1 (Type 2A): Onset of symptoms typically around 1–2 years.
3. Juvenile GM1 (Type 2B): Onset of symptoms typically around age 2–3 with reports of up to 10 years of age.

Symptom presence, severity, and rate of decline vary across and within the three pediatric subtypes. Type 1 features include coarse facial features, developmental delays and cognitive impairment, central nervous system dysfunction, including hypotonia and heightened startle reflex, and skeletal dysplasia (Lang et al., 2020; Regier et al., 2013). 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 (Regier et al., 2013). Other features reported across subtypes include seizures, gastrointestinal symptoms, such as constipation, impaired muscle tone and mobility, choking; and aspiration (Nicoli et al., 2021; Rha et al., 2021; Sperb et al., 2013). Cherry red spots are found in the macula of the eye in some children with GM1 and are more commonly found in children with Type 1 (Jarnes-Utz et al., 2017).

The expected lifespan of children with Types 1, 2A, and 2B is 2–3 years of age, 5–10 years of age, and young to middle adulthood, respectively (Nicoli et al., 2021; Regier et al., 2013). There is also an adult-onset subtype of GM1, which will not be explored in this study due to differences in symptom presentation.

There are no approved therapies for GM1. Therapeutic strategies that have been, or are currently being researched include substrate reduction therapy, enzyme enhancement therapy (using molecular chaperone therapy), and gene therapy (Nicoli et al., 2021; Rha et al., 2021). Barriers to treatment development include delayed diagnosis, determination of meaningful outcome measures to evaluate potential therapies, and achieving adequate bioavailability of the treatment to the central nervous system (Jarnes-Utz et al., 2017; Rha et al., 2021).

Prior research describes the natural history of GM1 in eight patients with infantile GM1, five patients with late infantile GM1, and eight patients with juvenile GM1 (Jarnes-Utz et al., 2017; King et al., 2020). There are no studies, however, evaluating the concerns of caregivers of children with GM1 regarding the impact of GM1 on their children and the burden of GM1 symptoms on the caregiver. In addition, there are no studies that can be used to inform the selection of trial outcome measures that are most meaningful to caregivers and—by extension—are expected to be meaningful to patients (Jarnes-Utz et al., 2017). The objective of this study is to describe the unmet treatment needs of children with GM1 and identify priority symptoms to treat, as characterized by primary caregivers of children with GM1. Relevant U.S. Food and Drug Administration guidance documents on patient-focused drug development (U.S. Food & Drug, 2022), which emphasize the importance of incorporating patient/caregiver experience, priority, and preference data in medical drug development, informed the conceptualization and implementation of this study. The objective of this original research on GM1 is to inform patient-focused drug development by characterizing meaningful and prioritized symptom targets, which will also inform the identification of clinical trial endpoints and outcome measures.

2 | METHODS

2.1 | Approach and aims

This study was conducted in two sequential parts, both of which used a mixed-methods approach that was qualitatively driven. Our approach was developed to account for the small sample sizes in ultra-rare disease research, the existence of GM1 subtypes and symptom heterogeneity between and within subtypes, and the anticipated variable stages of progression and ages of children with GM1, which we expected to influence respondents' current experiences and priorities. Part 1 comprised a brief survey followed by focus groups of parents of children with GM1. Part 2 included a survey followed by one-on-one interviews. The aim of Part 1 was to explore GM1 disease burden, as well as the features and symptoms with greatest impact on the child and family. The aim of Part 2 was to build upon Part 1, exploring the most important and impactful GM1 features and symptoms to treat. Both parts separated and differentiated the GM1 subtypes in the data collection and explored concepts that are not included in this report.

This study was sponsored and led by the Cure GM1 Foundation, with collaboration from the National Tay-Sachs & Allied Diseases Association (NTSAD). Both organizations are headquartered in the United States but serve families across the globe. Research expertise and analysis was provided by RTI International. The study was informed by a multidisciplinary advisory committee of academic and industry researchers, specialist physicians, and parents. The advisory committee reviewed and refined the study aims and instruments, reviewed and responded to emerging results, and those on the authoring list reviewed and commented on this report.

2.1.1 | Inclusion and recruitment

Parents or primary caregivers of children with GM1 were eligible to participate; all participants were biological parents or stepparents; thus, we use the term "parent" throughout. Affected children were diagnosed at least 3 months prior to participation. Bereaved parents were eligible to participate if their child had died within the past 36 months. Only one parent in a parenting dyad (e.g., the mother and father of one child) was allowed to participate in the same part; participation of two parents in a dyad was allowed across parts (i.e., one parent could participate in the focus group part and another in the interview part). Parents had to be able to participate in English language data collection (Part 1) or in English or Portuguese (Part 2). As this study sought to better understand the perspective of the caregivers for individuals with a pediatric phenotype of GM1, parents of individuals with adult-onset GM1 were excluded from the study and individuals who themselves have a diagnosis of GM1 were excluded from the study.

In Part 1, parents participated in one of three focus groups that were limited to a single GM1 subtype. Participants in Part 2 responded to overlapping but distinct questions based on the child's GM1 subtype. Parents self-reported their child's GM1 subtype. All participants

provided consent online prior to completing the survey and verbally prior to completing the focus group.

Recruitment was conducted by the Cure GM1 Foundation and NTSAD using direct outreach and social media. Participants were provided a $20 USD incentive or the Brazilian equivalent for their participation. Both parts of the study were approved by the Institutional Review Board at RTI International.

2.1.2 | Instruments and procedures

Part 1 began with a brief survey in REDCap to characterize the child's GM1 subtype, obtain a brief GM1 history, and collect basic demographics. This was followed by three moderated focus groups conducted in May and June 2021 that included 3–5 parents in each group. The groups were conducted via Zoom videoconferencing. Groups were moderated by an experienced researcher using a focus group guide, with another experienced researcher to observe each group, take high-level notes, and ask clarifying questions as needed. Focus group topics included: exploration of GM1 features or symptoms with the greatest impact on the child; symptoms with the greatest impact on the parent/caregivers and symptoms with the greatest impact on the entire family. Participants were then asked to imagine a non-curative treatment and describe small but meaningful and important changes to their child's symptoms that they would want to achieve. Because we anticipated that stage of progression would influence responses, we asked parents to respond to focus group questions based on their child's current status, but to also think back and ahead. Focus groups lasted approximately 90 min.

Results from Part 1 informed the Part 2 interview guide and the addition of an object-case best-worst scaling (BWS) prioritization activity to the Part 2 pre-interview REDCap survey (which was also translated into Portuguese). BWS is a stated preference method designed to obtain ranking and relative importance data by asking participants to choose the most and least desirable options across a series of questions (Flynn, 2010; Najafzadeh et al., 2018); here, in each question we asked parents to indicate the "most important" and "least important" symptoms to treat out of five symptoms/features of GM1 in the context of a non-curative treatment. The GM1 symptoms/features were developed based on focus group responses; separate lists were developed for Types 1 and 2A/2B. Items were reviewed and refined by the study advisory committee. The research team conducted user testing with three parents of children with GM1 for clarity and acceptability of the BWS activity. Tables 5 and 6 show symptoms used in the BWS activity for Types 1 and 2A/2B, respectively.

We selected BWS because it can result in individual-level as well as aggregated ranking data. Goals of including a quantitative prioritization component were to facilitate participant deliberation about their current priorities, target and structure the qualitative exploration, and report on aggregate results. The interviewers employed a semi-structured interview guide and a visual representation of each respondent's ranking to explore the impact of GM1 on the respondent and their child, agreement with individual-level BWS activity results, rationale for symptom rankings, and the impact of child age and stage of GM1 regression on symptom importance. Individual ranking results were used to focus the interview discussion—first on exploration of the highest-prioritized symptoms, followed by the lowest-prioritized symptoms. Parents were asked to provide rationale for each symptom, describe how that symptom presented in their child, and discuss the impact of symptoms on the child and their families. Similar to the focus group approach, we asked respondents to respond based on their child's current status, but to also think back and ahead when answering questions about their symptom priorities. Participants were permitted to re-think their priorities during the interview and were prompted to provide more detail if they described symptoms as being related to or dependent on each other.

Part 2 interviews were conducted via Zoom between December 2021 and March 2022. Interviews lasted approximately 60 min and were conducted in English or Portuguese by two trained interviewers, one of whom is fluent in Portuguese.

2.2 | Analysis

2.2.1 | Part 1

The REDCap data were analyzed descriptively by a research analyst. A study investigator created structured debrief reports for each focus group. Each focus group was audio-recorded and transcribed using a computerized transcription program (Temi). Transcripts were coded and analyzed using a standard approach to qualitative content analysis (Saldaña, 2009). Coding was completed by a trained and experienced qualitative analyst in NVivo using a codebook developed from the focus group moderator guide and study aims. The codebook was reviewed and refined by two investigators prior to implementation. The research team compared the debrief reports with qualitative content analysis from coding for quality assurance. Two investigators and the study PI (Peay) determined the final interpretation. Upon completion of analysis of all focus groups, researchers developed two lists of GM1 symptoms that were most important to treat. One list reflected the experiences reported by parents of children with Types 2A and 2B and the other list reflected the experiences of parents of children with Type 1.

2.2.2 | Part 2

The REDCap data were analyzed descriptively by a research analyst. Individual BWS rankings were calculated using BWS simple scoring (Peay et al., 2016) based on the difference between the number of times the participant selected a symptom as "most important" and the number of times the participant selected the symptom as "least important"; the same approach was used to calculate the aggregate rankings that are reported here. English language interviews were transcribed using a computerized transcription program (Temi); Portuguese language interviews were transcribed by a study team member fluent in Portuguese. Transcripts were analyzed by three experienced qualitative analysts using a rapid analysis process (RAP) in Excel (Taylor et al., 2018). Domains, or content categories, were determined

from the interview guide and study aims, and were organized into a matrix to allow analysis of domains by participant and across participants. Each row in the matrix represented one participant, creating a condensed narrative of their experience with GM1. Each column of the matrix represented a domain that correlated to a section or topic in the interview. Coding consisted of assigning summarized content from transcripts to domains within the RAP matrix. The quantitative data from the BWS activity for each participant was also included to allow triangulation of quantitative survey results and qualitative interview data. Two analysts piloted the draft RAP matrix using the same two transcripts to refine the domain coding definitions. The remaining coding was divided among three analysts, and the final interpretation determined by the three analysts and the study PI (Peay). All qualitative analysts involved in coding and interpretation immersed themselves in the data.

3 | RESULTS

3.1 | Part 1 results: Focus group participants

Participating parents ($n = 13$) originated from multiple countries in North America ($n = 9$) and Europe ($n = 4$). Tables 1 and 2 report on characteristics of caregiver respondents and their respective children with GM1. For those who had more than one affected child, information is shown for the oldest child.

TABLE 1 Respondent (parent) characteristics, focus groups ($n = 13$)

	Median	Range
Participant age (years)	40	(32–63)
	Count	Percentage (%)
Gender		
Female	9	69
Male	4	31
Marital status		
Married/partnered	12	92
Single	1	8
Self-reported race (select all that apply)		
White	12	92
Asian	1	8
Self-reported ethnicity		
Hispanic or Latino	1	8
Not Hispanic or Latino	11	85
No response	1	8
Education		
High school graduate	2	15
Some college, did not graduate	2	15
Associate's degree	2	15
Bachelor's degree	3	23
More than a bachelor's degree	4	31

3.2 | Part 1 results: Symptoms with greatest impact as reported by focus group participants

The focus group analysis generated a broad range of GM1 symptoms that caregivers reported having considerable impact on the child and family. During their respective focus groups, caregivers of children with Types 2A and 2B reported similar symptoms with greatest impact. These were GM1 effects on communication, particularly expressive communication; gross motor skills, described as the ability to get around, reposition oneself, and to avoid falls; muscle tone, including hypotonia and spasticity; fine motor skills, such as self-feeding and grasping; the ability to eat and swallow; seizures; sleep; and toileting.

Symptoms of greatest impact reported by parents of children with early infantile GM1 (Type 1) were communication; awareness of and engagement with caregivers; hypotonia or hypertonia; basic gross motor skills, such as head control and sitting; eyesight; hearing; feeding; seizures; and frequent illness.

Respondents in all GM1 groups reported pain as an important feature. Pain was described as both a challenging symptom to treat and a source of parental worry, as parents feared that the child was

TABLE 2 Oldest child with GM1-gangliosidosis (GM1) characteristics, focus groups ($n = 13$)

Number of children with GM1 by type	Count	
Type 1—Early infantile	3	
Type 2A—Late infantile	6	
Type 2B—Juvenile	4	
Number of children with GM1 by gender	Count	
Female	8	
Male	5	
Current age of oldest child with GM1/age at death (all subtypes)	Median	Range
Age of oldest living child ($n = 10$)	10 years	10 months–33 years
For deceased children: Age of child at death ($n = 3$)	3 years	2–10 years
Age at first concerns about development	Median	Range
Type 1—Early infantile	2 months	2–4
Type 2A—Late infantile	2 years	1–2 years
Type 2B—Juvenile	4 years	3–5 years
Age at diagnosis	Median	Range
Type 1—Early infantile	6 months	6–10 months
Type 2A—Late infantile	3 years	2–10 years
Type 2B—Juvenile	10 years	5–12 years
Time between symptom onset and diagnosis	Median	Range
Type 1—Early infantile	4 months	2–8 months
Type 2A—Late infantile	1 year	1–8 years
Type 2B—Juvenile	4 years	3–6 years

experiencing pain that they were unable to communicate to their caregivers. Parents frequently referred to other impacts on the child, such as safety concerns associated with falls, secondary to impairments in gross motor skills. Parents, especially those of children with Types 2A and 2B, also described both parental and child distress associated with the child's regression in many previously acquired skills.

In defining their priority symptoms, parents indicated that they weighed impact based on the reduction in their perception of the child's quality of life (QoL). Some symptoms, such as toileting, were reported to have a larger impact on the caregivers' QoL than the child's and were thus considered to be less important. Although some parents acknowledged that the symptoms with greatest impact on their child were different from the symptoms that most impacted them as parents, when it came to prioritizing symptoms for treatment, most parents agreed, "what's hardest on the kids is hardest on you."

3.3 | Part 2 results: Interview participants

About 26 parents participated in the interview part of the study, with interviews conducted in either English ($n = 22$) or Brazilian Portuguese ($n = 4$; all parents of children with Type 1). Nine parents reported that their child had Type 1, nine reported Type 2A, and eight reported Type 2B. Participating parents originated from multiple countries in North America ($n = 14$), Brazil ($n = 4$), Europe ($n = 4$), Australia ($n = 2$), and Southeast Asia ($n = 2$). Tables 3 and 4 show characteristics of the participants and their children with GM1; for those that had more than one affected child, information on the oldest child is shown.

TABLE 3 Interview participant characteristics ($n = 26$)

	Median	Range
Participant age (years)	37	26–59
	Count	Percentage (%)
Gender		
Male	11	42
Female	15	58
Marital status		
Married/partnered	24	92
Separated/divorced	2	8
Self-reported race (select all that apply)		
Black	1	4
Asian	3	12
White	22	85
Other	3	12
Self-reported ethnicity		
Hispanic or Latino	3	12
Not Hispanic or Latino	20	77
Missing	2	8
Prefer not to say	1	4
Education		
High school graduate	4	15
Some college, did not graduate	4	15
Associate's degree	2	8
Bachelor's degree	7	27
More than a bachelor's degree	9	35

3.4 | Part 2 results: Most important symptoms to treat

3.4.1 | Pre-interview symptom prioritization activity

Based on the focus groups, two lists of high priority symptoms (one for Type 1 and the other for Types 2A and 2B) were developed for

TABLE 4 Interviews: Oldest child with GM1-gangliosidosis (GM1) characteristics ($n = 26$)

Number of children with GM1 by type	**Count**	
Type 1—Early infantile	9	
Type 2A—Late infantile	9	
Type 2B—Juvenile	8	
Number of children with GM1 by gender	**Count**	
Female	10	
Male	16	
Current age of oldest child with GM1/age at death (all subtypes)	**Median**	**Range**
Age of oldest living child ($n = 21$)	7 years	1–33 years
For deceased children: Age of child at death ($n = 5$)	1 year	5 months–11 years
Age at first concerns about development	**Median**	**Range**
Type 1—Early infantile	4 months	1 month–1 year
Type 2A—Late infantile	1 year	7 months–2 years
Type 2B—Juvenile	4 years	2–5 years
Age of child at diagnosis	**Median**	**Range**
Type 1—Early infantile	10 months	1 month–2 years
Type 2A—Late infantile	2 years	1–5 years
Type 2B—Juvenile	10 years	4–12 years
Time between symptom onset and age at diagnosis	**Median**	**Range[a]**
Type 1—Early infantile	5 months	0–12 months
Type 2A—Late infantile	1 year	0–4 years
Type 2B—Juvenile	6 years	2–8 years

[a]0 indicates no time difference reported between first symptoms and age at diagnosis.

TABLE 5 GM1-gangliosidosis Type 1: Pre-interview prioritization activity using best-worst scaling to rank importance of features/symptoms to treat ($n = 9$)

"Importance to treat" ranking of feature/symptoms
• Lifespan[a]
• Child expressing needs/wants[a]
• Pain/discomfort
• Eating/feeding
• Muscle tone
• Moving his/her body
• Senses: vision and hearing
• Child's awareness of environment and caregivers
• Fine motor skills/grasp and hold

[a]These items were tied, yielding the same mean priority score.

TABLE 6 GM1-gangliosidosis Types 2A and 2B: Pre-interview prioritization activity using best-worst scaling to rank importance of features/symptoms to treat

"Importance to treat" ranking of feature/symptoms	
Type 2A ($n = 9$)	**Type 2B ($n = 8$)**
• Lifespan	• Child expressing needs/wants
• Child expressing needs/wants	• Lifespan
• Getting around/mobility	• Getting around/mobility
• Eating/feeding	• Pain/discomfort
• Pain/discomfort	• Fine motor skills/grasp and hold
• Child reacting to environment and caregivers	• Eating/feeding
• Seizures	• Child reacting to environment and caregivers
• Fine motor skills/grasp and hold	• Clumsy/falls
• Muscle tone	• Seizures
• Clumsy/falls	• Sleep
• Sleep	• Muscle tone

the interview part. The aggregated order of symptom priority (defined as more or less important to treat) based on the BWS activity is shown in Tables 5 and 6. Symptoms in the tables are displayed from most important to treat (top) to least important to treat (bottom).

3.4.2 | Parental discussion on the symptom prioritization activity

Respondents across all subtypes indicated that most or all of the symptom items were highly important to treat. When deliberating during the interviews on their own pre-interview rankings, most respondents had difficulty determining which would be most important to treat. Parents sometimes opted to change their pre-interview symptom ranking based on the context of the interview questions. Many respondents reflected on the importance of their child's age and stage of progression on symptom priorities (i.e., their priorities would change at different times in the child's life). Additionally, parents often discussed symptoms as interrelated—they perceived that an exacerbation of one inevitably led to the worsening of another. As one parent of a child with Type 1 described:

> It's tough because she's so little. Part of me wonders, when she gets older will she communicate more? Is she just still young?....The fine motor too; when you put it like that and I think about her everyday life, her being able to hold a spoon, her being able to hold a cup, her being able to hold a teddy, her being able to hold a toy—those things are significant too. I don't know if I could put that above her being in pain. I don't know if I could put that above her being able to talk, right? This is where it becomes so tough. This is such a nasty disease. It really is. It's so hard to pick between these things, I wish I could give her all of them... I hope a drug gets made that [has] all of these things.

Further, respondents articulated the challenge of the pre-interview ranking activity due to the symptom heterogeneity among children with GM1. Some parents indicated that they did not select a symptom at all if their child did not currently experience the symptom, causing the symptom to appear in the middle of their ranking. This contrasted to other parents who selected symptoms their child was not currently experiencing as least important, causing those symptoms to appear at the bottom of the ranking. These challenges were anticipated and led to our selection of a mixed-methods design.

A summary of parent responses regarding the importance of each symptom is shown in Table 7. The table reflects qualitative differences in responses based on GM1 subtype.

An overarching finding was that respondents grouped certain types of GM1 symptoms as "all going together" and "interrelated." Respondents perceived that some symptoms could not logically be separated when determining relative importance. Thus, we report symptoms under four larger domains to capture the way that respondents most often characterized related symptoms: Interaction and Engagement, Lifespan/QoL, Muscle Function and Tone, and Eating/Feeding. The symptom "pain" was interspersed among these domains.

3.5 | Interaction and engagement domain

Many parents prioritized symptoms related to their child's ability to express themselves, perceive their environment, and interact with others.

The symptoms grouped under this domain include:

1. Child expressing own needs/wants
2. Child reacting to environment and caregivers (Types 2A/2B) and child awareness of environment and caregivers (Type 1)
3. Senses: vision and hearing (Type 1)

Symptoms that were described as interdependent or related included:

1. Pain/discomfort
2. Muscle tone
3. Getting around/mobility (Types 2A/2B) and moving his/her body (Type 1)

TABLE 7 Summary of parent responses on importance of GM1-gangliosidosis (GM1) features/symptoms

Feature/symptom	Presentation	Impact
Symptoms relating to GM1 Type 1		
Child's awareness of environment and caregivers	• Recognition of family/caregivers • Ability to interact and respond to stimuli • At end of life: Positive (feeling parents' love) and negative (feeling pain/discomfort)	• Required for child to feel supported/loved • Parents report innate need for their child to recognize them • Influences others' (e.g., health care providers, non-family caregivers) perceptions of child, impacting the attention and care the child receives
Moving his/her body	• Limited head control • Limited use of arms/hands • Lack of achieving early milestones (e.g., sit or roll over) or regression	• Limits even basic autonomy/independence • Limited ability to self-correct for discomfort • Associated with health impacts (e.g., movement helps dislodge mucus and prevent pneumonia)
Senses: vision and hearing	• Reacting to sound • Following with gaze • Regression over time	• Supports child's ability to interact and recognize parents/caregivers • Important for child to feel protected/comforted by caregivers
Symptoms relating to GM1 Types 2A and 2B		
Child reacting to environment and caregivers	• Connecting with and developing relationships with caregivers and others • Parents reported that significant regression does not happen until later in disease course, especially with Type 2B	• Enables parents to provide better quality care • Enhances child/caregiver relationship • Allows child to make meaningful connection with others (e.g., siblings)
Clumsy/falls	• Ambulation or other mobility attempts lead to falls	• Causes injuries • Requires caregiver vigilance • Limited relevance to non-ambulatory children; more relevant for Type 2B than 2A • Consistently described as less important than other symptoms
Getting around/mobility	• Type 2A: Few children could walk, although some were previously ambulatory; many could crawl • Type 2B: Most children could walk, stand, or crawl; some require aids • For children who could not walk parents wished they could sit independently	• Movement (e.g., exercising, standing straight) enhances health and QoL • Associated with child independence and participation in daily activities • Inability to perform a skill, especially something the child used to be able to do, can cause child frustration • Loss of mobility increases care burden • Parents of children with Type 2B expected that regression in mobility would cause greater impact in the future
Seizures	• Parents reported a range of frequency and severity of seizures • Parents reported mixed success at management via medication and diet • Type 2A: Many children did not experience seizures; parents reported interference with daily activities for those who did • Type 2B: Some children used to have seizures but they are now managed; a few have poorly controlled seizures	• The few parents who reported high impact on daily life had children with frequent, daily, and debilitating seizures • Parents whose children did not currently experience seizures reported anxiety about potential onset and that seizures would be important to treat if their child developed them
Sleep	• Few parents described impactful sleep symptoms in comparison to other GM1 symptoms	• Sleep issues are manageable (e.g., through medication) or easier to tolerate than other symptoms
Symptoms relating to GM1 Types 1, 2A, and 2B		
Child expressing own needs/wants	• Type 1: Parents gauged child's expressions/cues/reactions to determine needs/wants • Types 2A and 2B: With regression in speech, parents increasingly relied on nonverbal cues	• Required to allow caregivers to meet the child's basic needs (all types) • Required to communicate pain (all types) • Enabled child to express choices (all types) • Enabled child to interact with others (all types)

TABLE 7 (Continued)

Feature/symptom	Presentation	Impact
	• All types: Parents described employing mental checklists or process of elimination to determine needs, with mixed success • More difficult for non-parents/regular caregivers to determine child's needs/wants	• Inability to express needs/wants led to child frustration (particularly Type 2B)
Eating/feeding	• Type 1: Common for eating/feeding to be a current or past high priority; almost all children used gastrostomy tube (G-tubes) • Type 2A: Most did not have current issues, but a few had challenges swallowing and chewing and were more likely to use a G-tube use than children with type 2B • Type 2B: Children mostly fed themselves, with some challenges; some reported G-tube use	• Risks of choking, aspiration, pneumonia, or hospitalization (all types); Type 2B parents described aspiration as traumatic for child • Eating was not as enjoyable for the child as parents thought it should be (all types) • Self-feeding/eating by mouth was associated with child independence (Types 2A and 2B) • Restrictive diets (e.g., ketogenic, dairy-free, purees) were limiting to child and placed a high burden on caregivers • Low impact reported by parents whose children had no current feeding issues or who were satisfied using a G-tube
Fine motor skills/ grasp and hold	• Type 1: Children had limited, declining, or no ability to grab/hold objects • Types 2A/2B: Most children had no regression or moderate regression in these skills	• Associated with preserving child independence • Decline reduced child's self-care abilities (particularly relevant to Type 2B) • Most parents of children with Type 1 reported less overall impact compared to many other symptoms
Lifespan	• Parents highly aware of the life-limiting nature of GM1 • Parents interpreted this feature as extending lifespan but not necessarily achieving a normal span • Parents wanted more time with their children but were still more focused on pain management and ensuring their child's happiness • A few Type 2B parents expressed concern about care if their child outlived them	• Lifespan of children with GM1 is short and unpredictable; causes uncertainty and worry • Lifespan was not meaningful without QoL (all types) • Desire to extend life dependent on child happiness, presence of pain, current child's skillset, and stage of regression (all types)
Muscle tone	• Most children (all types) had more significant issues with hypotonia, but hypertonia was also reported • Type 1: Children were weak, had low tone, and limited ability to move limbs, sit up, and hold their head up • Type 2A: Children had low tone, declined strength, and ability to maintain body position • Type 2B: Most children's muscle tone was sufficiently managed through therapies; one parent reported significant challenges with tone	• Required for even basic mobility and self-care • Allows for greater child independence and participation in activities • Closely tied to skills associated with other symptoms
Pain/discomfort	• Type 1: parents reported no/modest pain, but many parents' goal was to reduce discomfort experienced by their child; discomfort was associated with inability to move, digestive issues, etc. • Types 2A/2B: Most children were not currently experiencing pain; it was a priority for the child to be able to communicate pain; discomfort was particularly associated with reduced mobility	• Managing child pain was a priority and necessary for child QoL • Pain can be difficult to distinguish in non-verbal children, resulting in parental anxiety about unidentified pain

Abbreviation: QoL, quality of life.

Although "child expressing needs/wants" was the most prioritized symptom in this domain across all GM1 subtypes, this symptom was discussed by parents as being interdependent with a number of other symptoms in a way that reflected an overall value of the child's ability to engage with others and the world. Specifically, many parents discussed the child's reaction to their environment and caregivers (item shown to Types 2A and 2B), the child's awareness of their environment and caregivers (item shown to Type 1), or senses (item shown to Type 1) as being integral to the child's ability to express needs and wants. For example, being able to see is a prerequisite for the child tracking a caregiver with their gaze, which is both a way to react to caregivers and a mechanism for basic communication.

Parents also discussed how muscle function and tone were necessary to support communication modalities, including controlling one's eye gaze, ability to use one's tongue in speech, doing sign-language, reaching/grabbing, and pointing. Interaction and engagement symptoms were also described as related to pain and discomfort, which were discussed as among the most important things a child may need to express. For example, a parent of a child with Type 1 described her rationale for prioritizing senses and muscle tone to support the child's ability to interact:

> The senses, vision and hearing, and muscle tone are definitely the most important because those things I think would lead naturally to a child being able to express their needs and their wants because they're gonna be able to participate in their life more…. When I thought about a child expressing needs and wants, I've thought about, that is their ability to communicate. So that's kind of like them being able to talk or maybe sign or just grab things for themselves or just like interact with their environment more… How would you know that they cared about their environment if they didn't have the senses and the muscle tone and the expression?

3.5.1 | Rationale

These symptoms were reported as affecting the child's health and quality of caregiving, social well-being, and ability to express emotions and preferences—all aspects that parents tied to their perception of overall QoL.

3.5.2 | Quality of caregiving

Parents discussed their child's ability to effectively communicate, whether verbally or through movement, as critical to the caregivers' responsibility to meet the child's basic needs, such as food, toileting, and pain management. In the absence of the child's ability to communicate needs or a source of pain, parents described that they must sometimes guess what is wrong or go through a "mental checklist" of what the child may need, potentially prolonging the child's discomfort and frustrating both parent and child. One parent (Type 1) said:

> "I think the biggest thing is that he can't tell us what's going on and sometimes not being able to know makes it even harder."

Parents felt this domain was the key facilitator of quality caregiving.

3.5.3 | Social well-being

Parents expressed concern that a child's loss of the ability to engage with others would lead to fewer meaningful interactions and social isolation. For example, a parent (Type 1) described that other people do not speak or pay attention to her child because they do not think the child will understand. Another parent (Type 2B) described the value of social relationships to her child:

> "He likes people. He likes being around them and with them, and having better connection would bring a lot of value to him."

A parent (Type 2B) elaborated:

> "Being able to understand what's going on and keep that mental awareness, I think is just a huge part of quality of life… in my opinion, one of the biggest things."

Parents also described the importance of reciprocal interaction for the caregiving relationship. For example, one parent (Type 2B) described how social interactions reinforce emotional bonds with the caregiver:

> "When the child loses the ability to be affectionate… I think it changes how the caregiver reacts to them as well, which overall impacts their care. Because it does make it a little more difficult, maybe a little more removed than what it was before when the child could hug and kiss you and you know, would do stuff like that. So I feel like the child being able to react is vital because I feel like it enhances their care that they get from their caregiver and it keeps their caregiver plugged in and like it's not just a job."

3.5.4 | Emotions and preferences

Several parents prioritized symptoms related to Interaction and Engagement because they felt that the ability to express one's emotions and preferences for nonessential things is important to one's QoL. For example, parents described that it would be meaningful if their child could indicate preference for a specific TV show or a certain toy. Some parents discussed the communication of preference in relation to motor skills like controlled eye gaze or grasping objects. For example, a parent (Type 1) said:

> "I want her to express herself a little. I would like it if she tried to pick something up, that she was interested in, a toy."

Parents also wanted to be able to know if their child is happy or sad, particularly if the child had previously expressed emotions in response to people or their environments and later lost that ability. One parent (Type 2A) said:

> "Yeah, because right now her interaction is very, very muted…She expresses very little joy, every so often a laugh or a reaction from us, but for the most part, just kind of stares at you blankly…She used to smile and laugh, and she doesn't do that as much anymore. So if we could get that or bring that back. That would truly be very meaningful."

3.5.5 | Changes in prioritization of Interaction and Engagement symptoms over time

Because of their perceived impact on QoL across the lifespan, symptoms associated with Interaction and Engagement were described as high priority for treatment regardless of stage. When parents did indicate a change in prioritization over time, their responses often reflected different preferred timing for a non-curative intervention. For example, some parents described treatments affecting the child's ability to express needs and wants as more important in later stages, because the expected disease progression would make that ability more important at that time (e.g., indicating pain or preferences at late stages of GM1). But a few said that it would be better to treat this symptom early in the disease, indicating an assumption that if communication skills had already been lost, a new treatment would not be able to restore those skills. Similarly, a few parents of children with Type 1 indicated that it would be better to improve the child's awareness of caregivers early, because awareness in Type 1 is lost so quickly; however, they still indicated that they would value improvement in that symptom as the disease progressed.

3.6 | Lifespan/QoL domain

Lifespan was highly valued by many parents. Parents consistently interpreted a lifespan benefit to represent age at death that would exceed the expected lifespan for the GM1 subtype. Parents were willing to care for their children despite their progressive disabilities and viewed any extra time with them as a bonus. The knowledge that their children's lives would be shortened and the unknowns associated with when they would die was stressful and frightening for parents. One parent (Type 1) explained,

> For me, taking care of my child was not a bad thing, losing them was the bad thing. And so I think for me that was my determining factor. Like, how can I get more time? Even if I'm having to take care of him and he really can't do much, which treatments are gonna give me more time?

However, while parents desired more time with their child, they also did not want to prolong suffering, explaining that their ultimate goal was to ensure their child was comfortable and happy.

3.6.1 | Rationale

The high value parents placed on lifespan was contingent on many caveats related to the child's perceived QoL. Ultimately, regardless of how parents ranked lifespan, most parents agreed that QoL was equally or more important than lifespan. Parents were more likely to prioritize lifespan if their child had an acceptable level of skill that could be maintained and they could lead a relatively comfortable and happy life. As a parent (Type 2A) articulated:

> Of course I think any caring parent would want their child to live a long and healthy life. So for us, even though living with him day to day can be very exhausting, I think we would both agree. We would want him to live the longest life he could, as *long* as he's happy and as long as he's not in pain. I mean, if it gets to a point where he's in pain, he's not thriving, then that's a different situation.

Using similar rationale, parents who did not rank lifespan as a top symptom emphasized that lifespan was less meaningful than QoL, such as the parent (Type 2B) who said:

> I've stopped praying and asking God to let [child] live. I am to the point that it is selfish for me to want her to stay here. I would much rather suffer the pain of losing her to heaven than to watch her suffering and pain and not be able to do anything.

Parents factored in pain/discomfort when considering perceptions of their child's QoL. As stated by a parent of a child with Type 2B:

> I guess the biggest thing for me is she, she already can't do the things she wants to do and then having to hurt on top of it I think just intensifies the…whatever the negatives are in her life. So if we could keep her as comfortable as possible in the midst of everything she's lost or losing, I think…I mean, people talk about quality of life. I know there's not much she can do, but I think that's up there, top priority as far as quality of life, pain management.

3.6.2 | Changes in prioritization of lifespan/QoL over time

Most parents expressed that lifespan would become less important over time if or when the child's condition regressed to a state in which they felt that was an unacceptable QoL. Other parents explained the importance of lifespan would not change or would be even more important in the future. However, parents demonstrated ambiguity and discrepancy within their own responses about relative importance of lifespan and symptoms they directly associated with QoL in the future. Some parents also worried about their ability to provide high quality care for the child over a longer period. A few parents shared that lifespan was especially important when their child was first diagnosed, as shortened lifespan was one of the more shocking symptoms for parents to accept.

3.7 | Muscle function and tone domain

Parents across all GM1 subtypes prioritized symptoms related to their child's ability to move and to use their muscles to perform tasks.

The symptoms that parent respondents grouped under this domain include:

1. Getting around/mobility
2. Muscle tone
3. Fine motor skills/grasp and hold
4. Clumsy/falls
5. Moving his/her body (Type 1)

Symptoms that were described as interdependent or related included:

1. Eating/feeding
2. Pain/discomfort
3. Child expressing needs/wants
4. Child reacting to environment/caregivers (Type 2A/2B)

Although "getting around/mobility" was the most important symptom in this domain to parents of children with Types 2A and 2B and "muscle tone" was the most important to parents of children with Type 1, parents across all subtypes viewed symptoms related to muscle function as interrelated, as articulated by a parent (Type 2A):

> "When I was thinking clumsy and fall, I was thinking back to when she was walking and she would fall or, but she does fall sometimes when she's sitting…well, it goes with muscle tone. I mean, they all go together. They're all related."

Many parents of children with Type 1 discussed muscle tone in conjunction with head and neck control and the ability for the child to move and position their body. A few grouped muscle tone with eating/feeding, awareness of environment and caregivers, expressing needs/wants, and fine motor/grasp and hold. Parents explained that improved muscle tone would enable basic tasks like swallowing, grasping, and managing mucus secretions, as well as sitting up, which would allow the child to interact with others.

Although muscle tone ranked low overall among parents of children with Type 2A and 2B, several parents described it as very important to treat, reasoning that improving muscle tone would improve other symptoms. As one parent (Type 2B) explained:

> So muscle tone impacts everything, walking, for example. You say clumsy and falls, which is low to my mind, [because] if the muscle tone is fixed, then she's not going to be falling, right? Or most of the clumsiness comes because of the weak muscle tone. Right? So my thought process was if that's fixed, many of the other things will get fixed. I mean, even speech, which tends to be a big issue, maybe it's, you know, muscle tone of the tongue. That's where I was coming from.

3.7.1 | Rationale

Symptoms in the Muscle Function domain were described as important to parents because of their impact on activities of daily living, child independence and well-being, and impact on child's physical health and comfort.

3.7.2 | Activities of daily living

A few parents focused on mobility-related skills because they were skills that their children were in the process of losing, which directly impacted their daily life. These included the child's ability to walk, hold themselves, use fine motor skills, and avoid falling. These skills impacted the family's ability to travel and get around as well as the child's ability to complete self-care tasks (e.g., dressing themselves) and participate in family activities. One parent of a child with Type 2A explained that although her children could feed themselves, they had difficulty with food packaging and experienced challenges with other activities of daily living, such as brushing teeth and hair, writing, washing hands, dressing, and opening doors.

3.7.3 | Independence and well-being

Parents associated the child's ability to move—whether to walk, crawl, or use fine/gross motor skills to feed themselves—with child independence. Parents across all groups tied child independence to QoL and child enjoyment. One parent expressed concern about his child with Type 2B losing mobility, saying:

> Within the next few years, this [getting around] is going to be a really big issue for us as he's going to lose that ability, and really his independence, his ability to go play with the toys that he wants or go in the

> kitchen, looking for a snack or run around outside. And I feel like that just is a huge quality of life thing for him. You know, not that his life is meaningless without mobility, but it's just a huge part of his life right now, is that ability to get himself where he wants to be. So for me, his ability to be mobile independently is just a huge source of independence for him.

Another parent of children with Type 2A explained one of her children was

> "so much happier if he can stay on his knees or if he can kind of like be sitting up, but if his face is just in the ground and he is just like stuck, cuz if he's on the floor kind of playing on his own, like he's not having fun."

Similarly, a parent (Type 1) explained that if her child had increased muscle tone to sit up and control her head, then she could interact more with her sibling and others, resulting in greater "participation in life." Parents described how loss of independence led to child frustration, as described by one parent (Type 2A):

> "We kind of lost the ability for him to hold his sippy cup and drink it by himself. And I can tell he still has that thought process because like, when we get the cup in front of him, his hands will close and he doesn't make the motion like to his mouth, but his hands will close. So he remembers that I should grab this. And he gets frustrated at feeding time with the sippy cup."

Parents also described how loss of independence led to loss of self-esteem as children realized their differences and limitations compared to other children, despite parental efforts to create a life that was as normal as possible for their child. One parent of a child with Type 2A described her child comparing herself to her sister:

> "She sees sister doing things, walking and running… And you can see it on her face that she wants to do it. And she can't, and that is devastating. And she just wants to play with her sister… I mean, we make the best of it and we include her and everything, but she, you can just see it on her face like she's sad."

3.7.4 | Physical health and comfort

Some parents saw their child's ability to move as vital to their general health. For example, two parents of children with Type 1 explained that their children's inability to move impacted their pulmonary health and contributed to concerns such as aspiration and pneumonia. One parent said:

> He constantly got pneumonia and mainly it was because he couldn't move, he couldn't move good enough to get those obstructions outta the way. So I would say movement is probably the number one limiting factor as far as their quality of life and probably even their length of life.

Other parents of children with Types 2A and 2B explained that their children's clumsiness often led to injuries. Parents also expressed that their children would be more comfortable if they could scratch an itch, sit up, hold their head, turn themselves while sleeping, or cover themselves with a blanket. Some parents discussed their child's pain/discomfort in relation to their ability to move. As explained by a parent of a child with Type 1:

> "This part about muscle tone is very important because it causes a lot of discomfort to her. Even sometimes in our lap, there comes a time when she starts to feel uncomfortable….If you aren't holding her correctly, it's probably painful. So, this lack of muscle tone can cause it [pain/discomfort] also."

One parent (Type 2B) explained his child's ability to communicate pain to her physical therapist was dependent on using her foot to tap the therapist:

> In physical therapy one day, she was in pain, but she wasn't crying out. She wasn't showing the facial expression for pain, but she took her left foot up and actually raised it up and tapped the physical therapist on his arm and just kept tapping him gently but rapidly until he stopped massaging…. As soon as he stopped doing that, she put her leg back down. So he had no clue what was going on. I said, 'I think she's trying to tell you that's hurting.'

3.7.5 | Changes in prioritization of Muscle Function and Tone symptoms over time

Parents' prioritization of symptoms associated with the Muscle Function and Tone domain changed over time as skills regressed and as other symptoms emerged. For example, one parent who prioritized symptoms related to Muscle Function and Tone acknowledged that these symptoms would become relatively less important as communication-related skills or eating/feeding became more challenging, while another parent (Type 2A) explained that clumsiness was more important when the child could still ambulate. In contrast, another parent (Type 2B) explained that symptoms related to mobility would become even more important in the future because reduced mobility would require alterations to caregiving for the child. One parent of an older child with Type 2B explained that their priorities shifted as they came to accept the loss of the child's muscle tone over time:

> When he first started exhibiting [reduced muscle tone], that was a huge issue. It was off the charts, one of the biggest things that was very, very apparent and troubling to us. But it's not really an issue at this point. Not that he doesn't have it…but as far as priority and importance, it's not an important thing at this point cause back to what I mentioned earlier about acceptance, you know, just kind of the way it is. So it's okay. But…at the top of the list, him expressing his own needs and wants and reacting and connecting with people, those are high on the list. And I see that those are the things that he wants in his heart and…what's important to him at this point.

When asked, many parents (even those emphasizing the importance of symptoms related to Muscle Function and Tone) said they would choose to preserve Interaction and Engagement skills over Motor Function and Tone skills. However, one mother (Type 2A) explained that she would not want to preserve her child's cognition while letting muscle function decline, because her child would become increasingly aware of their worsening condition.

3.8 | Eating/feeding domain

Parents of children with all GM1 types acknowledged eating/feeding as a crucial aspect of daily life. Parents experienced varying levels of difficulty with eating/feeding, such as restrictive and burdensome diets (e.g., ketogenic, dairy-free) and long feeding times. Parents explained that their child's eating often depended on their ability to swallow and chew, which required proper muscle tone. Additionally, children required fine motor skills to self-feed.

Symptoms that were described as interdependent or related included:

1. Muscle tone
2. Fine motor/grasp and hold

3.8.1 | Rationale

Parents prioritized eating/feeding because of (1) its importance to growth and survival, and (2) the belief that eating/feeding should be enjoyable.

3.8.2 | Growth and survival

Parents recognized the importance of nutrition, growth, and strength, which they associated with successful eating/feeding. Parents also recognized how eating/feeding issues put the child at serious risk of choking and aspiration. For example, a few parents of children with Type 1 described that aspiration and choking on foods led to hospitalization, pneumonia, and malnourishment.

3.8.3 | Eating/feeding as a pleasurable and communal activity

Parents described eating/feeding as a foundational aspect of daily life and enjoyment of eating as a component of good child QoL. Perceived pleasurable aspects of eating/feeding included social interaction and eating of desired/preferred foods. Some parents reported that restrictive diets (e.g., ketogenic, dairy-free) or feeding measures and long feeding times frustrated the parent and hindered the child from engaging with others—for example, they had to abstain from eating because of G-tube use or eat different foods than others during school or family meals. Although many parents described transitioning to a G-tube as helpful in addressing eating/feeding-related challenges and were grateful for its availability, it also presented challenges. As one parent (Type 2A) explained,

> "It's just that thought of like enjoying your meals. For me…I enjoyed feeding him and having him eat, you could see he's happy with certain things that you feed him."

Some parents also described loss of enjoyment or anxiety associated with eating by mouth. For example, a parent of a child with Type 2B explained that her child would no longer eat certain foods that she associated with prior episodes of aspiration.

3.8.4 | Change in prioritization of eating/feeding over time

Many parents of children with Types 2A and 2B expressed that eating/feeding was more important when the child was younger and could still self-feed. Parents of children with G-tube placement reported that it helped the child stay nourished and avoid choking, and its use often shortened the previously long and challenging time it took for parents to feed their children. However, parents whose children still retained the ability to eat by mouth expressed hesitancy toward using a G-tube. Parents of babies or very young children with Type 1 anticipated eating/feeding to become more important in the future when they transitioned their children from milk and purees to solid foods, which their children may have difficulty chewing and swallowing.

3.9 | Characterization of other symptoms

Parents reported that all symptoms were important when thinking generally about the needs of children living with GM1. Although no single symptom was consistently chosen as least important by all parents, clumsiness, seizures, sleep, and muscle tone were frequently ranked lower than other symptoms by parents of children with Types 2A and 2B, and fine motor skills for Type 1.

3.9.1 | Rationale for lower priority symptoms

Symptoms ranked lower were ones that the child experienced less frequently, or for some children, not at all. For example, parents whose children had never experienced seizures ranked seizures as less important, whereas parents whose children had frequent or poorly controlled seizures ranked this symptom on the high end. Similarly, parents often reported symptoms as less important if their child still maintained the skill or abilities associated with the symptom. In contrast, sometimes lower-ranked symptoms reflected milestones the child had never reached or skills they no longer possessed—this was particularly relevant for Type 1. Some parents reported that they adapted to a symptom, and thus the symptom was currently less important to them. A parent of a child with Type 2B stated:

> Sleep, for example, we would rank that high because it's rare that she sleeps at normal times, but we've learned to live with it. We've learned to navigate through that…but these other things, lifespan, seizures, pain/discomfort, child expressing own needs and wants, those are things that would help us and make the caregiving much more effective for us.

Last, parents explained that some symptoms were less important to them because they could manage them through existing adaptions and interventions. These included medications for pain and seizures and the use of devices such as G-tubes. As described by one parent (Type 1A):

> "I would say they [symptoms ranked at the bottom] are important. They definitely affect your daily life and they're difficult, you know, it's something that every child with GM1 I think experiences, but I think that there are a lot of treatments available already for all of those things."

3.10 | Combined Part 1 and Part 2 results: Burden of GM1

Parents emphasized the significant impact GM1 has on their lives, their children's lives, and on their families. When describing the impact of GM1 on their child, many parents described their child's limitations, lack of independence, and dependency on caregivers for basic needs. Some parents described that their child became frustrated as symptoms progressed. Despite the devastating impact of the condition, most parents believed their child to be happy and cognitively present.

Parents described having to adapt their lifestyles to take care of their child, including negative impacts on their ability to work outside the home, do family activities, and travel outside the home. Parents also discussed positive and negative impacts of the condition on their other children without GM1. Parents reported mixed levels of social support, but most desired more education and support, including from health care providers and schools. Some parents described social isolation, which was exacerbated by the COVID-19 pandemic. Although parents were willing to do all they could to help their child, many described the time-consuming nature of their child's care. Parents of children who had progressed further in GM1 described additional caregiving challenges when basic reciprocal communication became limited.

A small number of parents described the physical toll of caring for a child with GM1, especially as they grew heavier and less mobile. Parents also described the specialized caregiving expertise required for a child with GM1. Several respondents wondered who would be able to adequately take care of their child if the parent was no longer able to provide primary caregiving, and some worried about care falling to the child's siblings.

Parents expressed that they carried an ongoing emotional burden associated with GM1. Parents reported initial difficulty coping with their child's diagnosis. Most described ongoing stress associated with GM1 and their child's health status, and many reported considerable anxiety about symptom exacerbation, disease progression, and the end-of-life period. One parent of a child with Type 1 explained that he and his wife took shifts to stay awake with their child, for fear the child would die if they were not constantly vigilant:

> "We tried to go to sleep, but knowing that he might… choke on secretions and so on, you will not sleep. So we prefer that someone will be awake and someone will rest…knowing the condition and knowing what can happen, we found that it was the best thing."

4 | DISCUSSION

This study is significant because it is the first research study to evaluate the concerns and perspectives of caregivers for children with GM1. Importantly, the findings of this study of 39 caregivers of children with GM1 underscores the unmet treatment needs associated with the rare neurodegenerative disease. Parents emphasized the significant impact GM1 has on their lives and their children's lives. When describing the impact of GM1 on their child, many parents described their child's progressive limitations, dependency on the parent for basic needs, and lack of independence. Respondents also reflected on the caregiving burden and major emotional toll that GM1 exacts from parents and others close to the child.

This study provides caregiver perspectives on the most important features and symptoms of GM1 to treat. Parents emphasized that the most important symptoms were those that were most burdensome to the child, not those that were most burdensome to the parents. Parents prioritized four domains comprising symptoms that they perceived to be interrelated: Engagement and Interaction, Lifespan/QoL, Muscle Function and Tone, and Eating/Feeding. As found in several studies on other serious pediatric conditions (Peay et al., 2014; Porter et al., 2021), ensuring an acceptable QoL for the child was paramount in parents' prioritization of symptoms. Parents described QoL 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, focusing on the ability to communicate wants/needs, prevent pain/discomfort, improve ability to get around, and enhance eating/feeding. Due to anticipated impact on

child QoL, respondents generally placed higher value on the basic cognitive functions that make up the Interaction and Engagement domain rather than the Muscle Function and Tone domain, yet both domains were described as important. Although lifespan was very highly valued, almost all parents would not desire a longer life without associated high QoL for the child. Importantly, the interview participants identified *all the symptoms* presented to them as being highly important to children living with GM1; this is not unexpected since those symptoms were generated from parent feedback on impactful symptoms during the focus groups.

Our mixed-methods approach was intended to account for heterogeneity within a variable and progressive disorder. Parents described that the most important symptoms to treat would change if their child was younger or older, at a different stage of regression, or if they had a different current skillset or parents perceived different QoL. The progression of GM1 varies across and within subtypes (Rha et al., 2021), resulting in further variance among parent experiences.

4.1 | Study strengths and limitations

We employed a mixed-methods, two-part approach in which symptom lists were generated during focus groups and then prioritized using BWS by a different group of caregivers who participated in interviews. This approach ensured that the symptoms presented in the BWS activity and subsequent interviews were impactful and meaningful. This resulted in fairly structured interviews focused on eliciting respondent reactions to their individual rankings and exploring the symptom items at the top and the bottom of the ranking list. It is possible that this approach resulted in us missing important symptoms or features that would have been generated during a less structured interview or if we had artificially limited exploration of the symptoms that tended to cluster in the middle of the importance ranking. In addition, though we anticipated challenges associated with both GM1 heterogeneity and the correlation among symptoms in the BWS prioritization, some respondents proposed to change their priority ranking during the interview part. The ability of the research team to explore and describe their rationale for change during the interviews is a strength of our mixed-methods approach.

Parents self-reported their child's GM1 subtype, history, and diagnosis. Parent-reported classification was not verified by the research team. Subtypes are delineated by age of symptom onset; however, parents in our study indicated relatively long duration between onset of symptoms and diagnosis, which is consistent with research indicating diagnostic delay (Lang et al., 2020). Our study reflects variation in child age and stage, which is both a strength and a limitation. Additional research with slightly larger sample sizes could build on this study to explore the nuanced changes that come with progression in each subtype of GM1.

Future research should attempt to include a more demographically representative sample. Due to feasibility limitations, our data collection was conducted in English (focus groups and interviews) and Portuguese (interviews), which excluded perspectives from parents who did not speak these languages. Despite this limitation, interview and focus group participants represented a range of countries. Variation in access to diagnostic, medical, and supportive services may have influenced respondents' responses. Participants were recruited by the Cure GM1 Foundation and NTSAD; thus, the sample may be biased to those who engage with disease-focused foundations.

In addition, our data may reflect recall bias, particularly for parents of children who died. Bereaved parents were asked to describe the impact and importance of symptoms their child experienced soon after diagnosis and throughout their lives. To mitigate recall bias, parents were only eligible to participate if their child had died within 3 months of data collection.

5 | CONCLUSION

GM1 is a devastating condition with high burden on affected children and their caregivers. There are no data available regarding parent/caregiver perspectives on pediatric-onset GM1. Caregiver experience and preference studies have been conducted for many other rare diseases with a goal of informing the development of novel drugs and targeted therapies (Bridges et al., 2015; Monnette et al., 2021; Morel et al., 2016; Peay et al., 2014, 2021). This first caregiver prioritization and impact study for pediatric GM1 addresses a crucial gap in describing and contextualizing caregiver priorities for the most important symptoms of GM1 to treat.

Our study will also inform the identification of meaningful clinical trial endpoints and associated outcome measures. Our study complements the Natural History of Gangliosidoses Study (Jarnes-Utz et al., 2017) that described the clinical progression of GM1 and included 21 children with GM1 and 24 children with the related condition GM2 (Tay-Sachs and Sandhoff diseases) (Jarnes-Utz et al., 2017; King et al., 2020). The authors highlight the importance of including these features in clinical trial outcome measures: ambulation, verbalization and communication, and caregiver-reported socialization. Augmenting natural history data with systematically-collected caregiver data provides a strong basis to guide new therapy development and, ultimately, contribute to unmet treatment needs.

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CONFLICT OF INTEREST

A. Bingaman, S. M. Andrews, and H. Peay are Employees for RTI International; supported by funding from the Cure GM1 Foundation. M. Trad is employee of Lysogene. R. Giugliani is Investigator,

Consultant, and/or Speaker fees received from Abeona, Allievex, Amicus, Avrobio, Azafaros, BioMarin, Chiesi, Cyclo, DASA, Denali, Idorsia, Inventiva, Janssen, JCR, Lysogene, Novartis, Paradigm, PassageBio, Protalix, PTC, RegenxBio, Sanofi, Sigilon, Sobi, Takeda, and Ultragenyx. R. Giorgino is Employee of Azafaros. J. Jarnes is Consulting work for WORLD Symposium, Passage Bio, Lysogene, Sio Gene Therapeutics, Azafaros, Sanofi, BioMarin Pharmaceutical, Takeda Pharmaceutical, Spark Therapeutics; Investigator for clinical trials for Lysogene, Sanofi, BioMarin Pharmaceutical, Amicus Therapeutics, Takeda Pharmaceutical; Global Principal Investigator for Passage Bio; Advisor for the Cure GM1 Foundation. V. Ballard was formerly an employee at Passage Bio, Inc. All other authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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