



Parent Experiences of Sanfilippo Syndrome Impact and Unmet Treatment Needs: A Qualitative Assessment

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ABSTRACT

Introduction: Sanfilippo syndrome (MPS III) is a rare, degenerative condition characterized by symptoms impacting cognitive ability, mobility, behavior, and quality of life. Currently there are no approved therapies for this severe life-limiting disease. Integrating patient and caregiver experience data into drug development

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and regulatory decision-making has become a priority of the Food and Drug Administration and rare disease patient communities.

Methods: This study assesses parents' perceptions of their child's Sanfilippo syndrome disease-related symptoms using a research approach that is consistent with the Center for Drug Evaluation and Research (CDER) guidance. This study was initiated by the Cure Sanfilippo Foundation, and all steps in the research process were informed by a multidisciplinary advisory committee, with an objective of informing biopharmaceutical companies and regulatory agencies. We explored caregiver burden, symptoms with greatest impact, and meaningful but unmet treatment needs. Data were collected from 25 parents through three focus groups and a questionnaire. Transcripts were coded and analyzed using inductive thematic analysis, and descriptive analysis of quantitative data was conducted.

Results: Participating parents' children ranged in age from 4 to 36 years. Participants endorsed high caregiving burden across all stages of the disease. Analysis revealed multiple domains of unmet need that impact child and family quality of life, including cognitive-behavioral challenges in communication, relationships, behavior, anxiety, and child safety; and physical health symptoms including sleep, pain, and mobility. Participants reported placing high value on incremental benefits targeting those

symptoms, and on a treatment that would slow or stop symptom progression.

Conclusion: Even modest treatment benefits for Sanfilippo syndrome were shown to be highly valued. Despite high caregiver burden, most parents expressed a willingness to “try anything,” including treatments with potentially high risk profiles, to maintain their child’s current state.

Keywords: Meaningful treatment benefit; MPS; Outcome measure; Patient experience data; Patient-focused drug development; Sanfilippo syndrome

Key Summary Points

Why carry out this study?

Sanfilippo syndrome (MPS III) is a rare, pediatric-onset, multi-symptom disorder with no approved therapies.

Integrating patient-focused drug development and the collection of patient experience data into drug development and regulatory decision-making by the Food and Drug Administration (FDA).

Our study objectives included (1) exploring caregiver perspectives on unmet treatment needs relating to managing the symptoms of Sanfilippo syndrome, and (2) describing what constitutes meaningful treatment benefits for children with Sanfilippo syndrome and their families.

What was learned from the study?

Parents reported high burden and high unmet treatment need across physical health and cognitive/behavioral/psychological domains, some with differential impact on the child and the caregivers.

Participants advocated for clinical trials that shift focus from primary cognitive outcomes to other multisystem endpoints, and perceptions of non-curative therapies revealed a preference for treatment options that stop or slow the disorder progression to maintain the child’s current function to ensure quality of life; thus parents express high risk tolerance and a desire for broader inclusion criteria for trials.

DIGITAL FEATURES

This article is published with digital features to facilitate understanding of the article. You can access the digital features on the article’s associated Figshare page. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13247372>.

INTRODUCTION

Mucopolysaccharidosis type III (MPS III, Sanfilippo syndrome) is a rare, degenerative condition that impacts early development and causes multi-system symptom progression and early death [1–6]. The four subtypes of Sanfilippo syndrome (types A–D) occur as a result of the inability to break down the glycosaminoglycan heparan sulfate [2, 3, 5]. Characteristic symptoms of Sanfilippo syndrome typically manifest between the ages of 2 and 6 years, but there is variability in the timing of presentation and disease progression between subtypes, as well as heterogeneity within subtypes [4, 5, 7, 8]. The earliest developmental symptoms exhibited by most children with Sanfilippo syndrome are delayed speech acquisition and mild motor delays [5, 9]. Central nervous system (CNS) manifestations predominate the evolving phenotype, particularly cognitive decline and behavioral issues that impair adaptive daily living function [2, 3, 9–11]. Behavioral symptoms, which wane with progressing cognitive impairment, include hyperactivity, anxiety, impulsivity, poor compliance, and aggressive

actions [12, 13]. Sleep disturbances, including frequent night waking and an inability to settle at bedtime, are also common symptoms [14–16].

Several studies have addressed the impact of this multi-system disorder on caregiving parents and families. Sanfilippo syndrome has a pervasive impact on family life, with a greater negative impact as the child's needs increase [17]. Caregivers of children with Sanfilippo syndrome have identified agitation, impulsivity, hyperactivity, difficulties in communication, and sleep disturbances as some of the most difficult behavioral challenges to manage [18]. Studies assessing the impact of the child's illness on the caregiver's psychosocial function identified high levels of anxiety, depression, and distress [19], a negative impact on a parent's quality of life [20], and a high prevalence of post-traumatic stress disorder [21].

To date, there are no approved therapies for Sanfilippo syndrome [1, 22]. Clinical trials are ongoing or planned to use therapeutic approaches that include gene therapy, enzyme replacement therapy, and hematopoietic stem cell therapy, among others [23–28]. Several trials recently failed to find significant evidence of improvement using neurocognitive outcome measures or were terminated by the sponsor as a management decision [29–31].

Little is known about caregivers' priorities for new therapy development for Sanfilippo syndrome. The collection and integration of patient experience data (and in the case of pediatric disorders, caregiver experience and proxy-reported patient experience) into drug development and regulatory decision-making have become a priority of the Food and Drug Administration (FDA) and other regulatory authorities and payers [32]. Incorporating the perspectives of patients and caregivers may accelerate the development of drugs and products, lead to the modernization of trial designs, and expand current product development programs [33]. Reflecting the importance of understanding caregiver perceptions, in 2019 the FDA and National Organization for Rare Disorders (NORD) hosted two Listening Sessions on Sanfilippo syndrome during which they engaged 13 caregivers about the impact of the

patient's disease on essential activities of daily living, the importance of preventing further decline, caregivers' risk tolerance, and attitudes about clinical trials [34, 35]. Summaries from these engagement sessions reported that caregivers most frequently desired to preserve communication, mobility, and sleep [27, 28]. At the time of the Listening Sessions, the study presented here was in process. Using a research approach that is consistent with the Center for Drug Evaluation and Research's (CDER) newly released guidance [36], this study provides rigorous qualitative data from a larger caregiver sample ($n = 25$) that is informative for medical product development and the FDA's desire to "listen" to the voice of the community. The outcome of the recent FDA caregiver engagement through the Listening Sessions [34, 35] complements our multistep caregiver study.

Study Objectives

The purpose of this study is to obtain data on perspectives and experiences of the Sanfilippo caregiver community to inform symptom targets for future therapeutic development, outcome measure selection, and regulatory decision-making. Our study aimed to explore parent-reported impact of Sanfilippo syndrome symptoms on the patient and family, which symptoms were most important to be addressed by future treatments, and what degree of treatment benefit would be considered meaningful. These data informed subsequent research led by the Cure Sanfilippo Foundation [37].

METHODS

We employed an approach tailored to a rare disease community and consistent with CDER's drafted guidance on advancing patient-focused drug development [36]. This study was developed with collaboration and support from an advisory committee comprising parents of children with Sanfilippo syndrome, clinicians, industry partners, and the Cure Sanfilippo Foundation. Three in-person focus groups were conducted over the course of 4 months. Each group began with a pen-and-paper

questionnaire to provide background context about the respondents and their affected children, followed by semi-structured focus group exploration of symptom impact on child and family, and culminating in a brief quantitative prioritization activity (not described here). Two focus groups were conducted at the August 2018 International MPS Symposium and the third was a stand-alone focus group conducted in September 2018 in a location in the region where multiple families lived.

Participants self-reported as being a primary caregiver for a child living with Sanfilippo syndrome type A, B, or C. All participants lived in the United States and spoke English as their primary language. Only one parent in a parenting dyad was included in the focus groups. Cure Sanfilippo Foundation recruited participants using email and social media, through the ConnectMPS Registry communication, and by snowball recruitment through existing formal and informal parent support networks. Written consent was obtained from all participants. This study was approved by the Institutional Review Board at RTI International.

Each focus group was led by a trained moderator and a second researcher who took notes and requested clarification as needed. The researchers involved in data collection were RTI International staff and were unknown to the participants prior to the focus groups. In the focus groups, the moderator elicited responses at the individual level while also encouraging discussion among parents to get a broader understanding of the range of experiences. The focus group guide is available as S1 Appendix. Participants were asked to describe caregiving perspectives and identify Sanfilippo syndrome symptoms that in their experience had the greatest impact on (1) their child with Sanfilippo syndrome, (2) themselves, and (3) their families. They were then asked to describe incremental, non-curative symptomatic treatment targets that would have significant impact on quality of life, and to describe their hopes for their children. This was followed by a component where participants had the opportunity to raise new, but related, topics. The total duration ranged from two to two and a half hours, including time to complete the questionnaire,

the focus group discussion, a brief prioritization activity (not described here), and a planned break. Focus group discussions were recorded and transcribed. In addition, the moderator and second investigator took detailed and summarizing notes during and after each focus group using a standardized format, consistent with social research methods [38].

The RTI International IRB approved STUDY0020238 under a Social/Behavioral or Non-Interventional Research protocol. The procedures used in this study adhere to the tenets of the Declaration of Helsinki. Written informed consent to participate and publish these data was obtained from all participants. No identifying information is included in the manuscript.

Analysis

Transcripts of the focus groups were analyzed using an inductive thematic approach, allowing key themes to emerge and be interpreted naturally from the data [39, 40]. A codebook was first developed based on the focus group guide and refined through data immersion with codes originating from the dominant categories influenced by frequency, pattern, and significance. The codes were then systematically applied to the entire data set using NVivo 12 software [41] by the first author (KP), who attended each of the three focus groups. The coding frame was developed between two coders, reviewed by the senior investigator, and refined through consensus after consideration of multiple possible meanings and how these fit within the emerging categories.

Conceptually similar codes were collated together to define overarching themes and domains. Interpretation of coding reports was supported by the standardized notes taken during and immediately after the focus groups. Transcripts were also read “horizontally,” which grouped segments of text by theme to assess the relationship between the different codes [42]. Reviewing transcripts horizontally allowed the investigators to assess how the parent-reported symptoms affected specific members of the family.

The emerging results from the coding process included a summary of the thematic

analyses. These findings were reported to the advisory committee for a stakeholder check-in and to allow opportunity for advisors and experts to provide input on interpretation [43]. The coding reports were then further interrogated and refined to develop the final thematic structure. By the end of this process, no new themes emerged and nothing new was added to the codebook, suggesting all the major themes had been captured. [44].

RESULTS

Each focus group comprised 8–9 parent participants who provided direct care to at least one living child with Sanfilippo syndrome, yielding a total sample of 25 participants across the three focus groups.

Participant Characteristics

Table 1 summarizes participants’ self-reported demographic information. Participants were noted to live in 17 different U.S. states, and ranged in age from 29 to 65 years, with a median age of 38 years. Nineteen participants were female. Twenty-four were biological parents,

Table 1 Caregiver participant demographics (*n* = 25)

Demographics of caregiver participants	Median	Range
Age (in years)	38	(29–65)
	Number	%
Relationship to child		
Biological parent	24	96%
Step-parent	1	4%
Sex		
Female	19	76%
Male	6	24%
Race/ethnicity		
Caucasian	23	92%
More than 1 race	2	8%

and one was a step-parent with active caregiving responsibilities. Parents provided demographic and clinical data on their oldest living child with Sanfilippo syndrome, as indicated in Table 2. These children ranged in age from 4 to 36 years, with a median age of 8 years. Participants’ children were diagnosed with Sanfilippo syndrome subtype A (17), subtype B (6), or subtype C (2). Five of the children had participated in a prior or ongoing clinical treatment trial, testing either an enzyme replacement therapy or a gene therapy.

Focus Group Results

All parents described a high burden of disease for their child with Sanfilippo syndrome, themselves, other caregivers, and other family members. Thematic analysis revealed two overarching impact domains: cognitive/behavioral/psychological and physical health. Within those domains, parents reported 14 primary themes related to unmet treatment needs (depicted in Table 3 and described in detail below). Parents reported that addressing any of these discrete features of Sanfilippo syndrome would reduce burden and improve quality of life for parents and children. The unmet needs were

Table 2 Characteristics of participants’ child with Sanfilippo syndrome

Oldest child with Sanfilippo syndrome	Median	Range
Age (in years)	8	(4–36)
	Number	%
Sanfilippo subtype		
Type A	17	68%
Type B	6	24%
Type C	2	8%
Type D	0	0%
Ever participated in a clinical treatment trial	5	20%

In the case of more than one affected child, characteristics reflect the oldest living child

Table 3 Domains and themes: unmet treatment needs

Domain	Symptoms	Most significant impact on...
Cognitive/behavioral/psychological impact	Communication	Child and family
	Relationship and social deficits	Family
	Frustration	Child
	Impulse control/aggressive behaviors	Family
	Hyperactivity	Child and family
	Unsafe behaviors	Family
	Anxiety/unhappiness in child	Child
	Sleep disturbance/nighttime waking ^a	Family
Physical health impact	Pain/headaches (experienced and anticipated)	Child and family
	Mobility	Child and family
	Sleep problems ^a	Child
	Illness/vulnerability to illness	Child and family
	Seizures	Child
	Feeding and maintaining nutrition	Child
	Digestive issues and toileting	Family

^a Sleep challenges were reported to have a physical impact on the child and psychological impact on the family

often reported to have a differential impact on parents, families, and the affected children (see Table 3).

Symptoms identified as imparting the greatest burden were often multidimensional. They were described as affecting relationships within the family, impacting the well-being of the child and others in the family, provoking pain or distress in the child and/or parent worry about unresolved pain or distress, and causing parents to question their ability to provide the best care to their child. In addition, parents described impacts of symptoms on peer relationships and the schooling environment.

Symptom Domain 1: Cognitive/Behavioral/Psychological Impact

Symptoms related to communication and problematic behaviors were commonly identified as conferring the highest burden and representing the most pressing unmet treatment need. This was true across the spectrum of disease progression, though parents' reports of specific manifestations and their realistic expectations of the potential magnitude of treatment effect under this domain varied based on the extent of their child's disease progression.

Communication and Relationships

Parents reported that their children's communication limitations in expressive, pragmatic, and receptive language skills were a significant

disease burden. Parents particularly described burden associated with their child's decreasing expressive language, e.g., their ability to let others know what they want, need, or feel. Communication limitations led to frustration and behavioral issues in the child and significantly impeded relationships with peers and, in some cases, with siblings. These challenges with communication also hindered respondents' primary parenting goals—to maintain, to the extent possible, the health and well-being of the affected child and meet the child's evolving needs. Many parents noted that their inability to understand their children's verbal and non-verbal messages caused a sense of helplessness, frustration, and distress. This led some participants to question their parenting efficacy and for some caused feelings of guilt. Further, some parents reported that their child's ability to engage in any form of reciprocal communication was important to maintaining relationships, and that even modest enhancement of interactions such as meaningful blinking or eye gaze would provide considerable benefit.

“If there was some way for her to be able to communicate what's going on...Even if it's just like blinks of the eyes. Or raise of the eyebrow or squeezing of the hand. Like how people sometimes say “I love you” with like three hand squeezes. Something that small can mean the world.” (FG 1)

Frustration, Hyperactivity, Impulse Control, and Aggressive Behaviors

Almost all parents described considerable caregiving burden due to problematic behaviors during times in disease progression when these symptoms were most prominent. Parents reported a progression of problematic behaviors that were often difficult for them to clearly differentiate. While these behaviors were primarily identified as temporally co-occurring with cognitive decline, parents described a cross-domain association. For example, parents recognized frustration as a challenge stemming from the inability to communicate needs but also from regression in mobility function. These behavioral challenges, however, had largely

resolved in the children who had progressed to later-stage Sanfilippo syndrome.

“I think the hardest thing... is the frustration. There are things she wants to do, things she sees her older sister do, things she wants to communicate, and she knows she's not, and then that's when we have melt-downs or hitting or biting.” (FG 2)

Unsafe Behaviors

Parents were highly impacted by safety concerns related to their children's behaviors. Most reported a current or past need to be constantly watchful for their child's well-being and the safety of others. Concerns about safety were primarily associated with symptoms of hyperactivity and impulse control. Parents reported considerable burden on themselves and family members associated with chronically maintaining this high degree of vigilance. Several participants expressed feelings of disappointment with their own parenting when their children were inadvertently exposed to harm even while under parental supervision. Parents of children who had significantly advanced in the disease course had reduced concerns in this domain, as their child's diminished mobility and function resulted in corresponding reductions in unsafe behaviors. However, those parents reported that unsafe behaviors had been highly challenging earlier in their children's lives.

“Because they have no sense of safety. So, my biggest example of that is I was outside with [child] watching her, and somehow, she still jumped off a play structure onto a concrete floor and we had to go to the ER in an ambulance, the whole bit, and so I feel like an awful mom.” (FG 2)

Behavioral issues impacted the family dynamic, as more attention was required to supervise and care for a child with Sanfilippo syndrome. Several parents mentioned the need for their typically developing children to gain independence more quickly than their peers and take on a supporting role to help with their siblings in response to behavioral challenges. Parents indicated that their own obligation to

anticipate challenging behaviors and mitigate situations that may lead to problematic behaviors was an ongoing stressor. Several parents described considerable worry about, and experiences of, the affected child physically harming siblings, peers, schoolmates, and caregivers. The parents attributed these behaviors to low impulse control and high frustration rather than actual desire to harm.

“So that’s the impulsivity too. Like ‘Oh, we’re going down the slide. Let’s go.’ And he’ll get excited, and he’ll flap his arms, and he’ll shove someone down the slide, and of course we get a report from school.... Well, [he] wasn’t hitting because he was mad. He was hitting because he was excited.” (FG 2)

Anxiety/Unhappiness

Parents experienced a reciprocal distress from seeing their child unhappy or anxious. Anxiety associated with change or new experiences was particularly burdensome for families in day-to-day life. They described struggling to identify ways for their child to maintain better psychological well-being. Most parents expressed the desire to participate in memory-making experiences and special milestone activities with their children with Sanfilippo syndrome, and yet some parents described major barriers in taking their children outside of highly familiar environments due to their children’s anxiety. In contrast, for children who were in a later stage of disease progression, parents indicated that these anxiety symptoms had either resolved or were no longer discernable to the caregiver.

“Anxiety has the biggest impact for her. I hate seeing her unhappy and scared.” (FG 1)

Sleep Disturbance/Nighttime Waking

Sleep disturbances were a commonly recognized symptom, and aspects of its impact fall under both domains. Many parents acknowledged that their own inadequate sleep impacted their day-to-day functioning. Parents cited reasons for their own lack of sleep that included the need to supervise the child to ensure safety at

night, lack of toilet training and frequent loose stools requiring the need to change and clean their child during the night, worries of their child having a seizure, and some had anxieties related to their child’s Sanfilippo that interrupted their sleep as well.

“My child sleeps in our room in a bed because she has seizures and she has sleep apnea, and I want to be able to hear her. One night she was in bed with me, and Dad was on a trip, and I kept waking up ‘cause I’m a real light sleeper, and I’m like, ‘She’s not breathing.’ And it would happen numerous times throughout the night.” (FG 3)

Symptom Domain 2: Physical Health Impact

Similar to Domain 1, the specific manifestations of symptoms vary over time based on Sanfilippo syndrome progression. The most commonly reported symptom under this domain was pain.

Pain

A significant theme was the challenge associated with identifying when a child is in pain, parental worry about current or future pain, and the inability of healthcare providers to adequately identify or manage pain. This theme has conceptual overlap with the communication challenges as well as behavioral issues relating to a child ‘acting out’ due to pain or discomfort. Pain was reported as particularly problematic in that it is a difficult symptom to identify causes of and treat appropriately in children with cognitive and communication impairments [45–47]. The most commonly reported type of pain was headache. Parents described that when their children were in pain, they would react with verbal outbursts, holding his or her hand over an eye or pressing their head into people or objects during the headache, or crying without solace.

“Even when she was younger, she would express pain, but you didn’t know where the pain was coming from. It was hard for her to locate where that pain might have

been, even though she had a really high pain tolerance.” (FG 3)

Mobility

Parents described limitations in their child’s mobility as having a great effect on their child, particularly in the mid-stage of disease progression. For children in that stage, mobility challenges were a major cause of frustration and impacted activities of daily living. Reduced mobility also increased the caregiving burden on parents. Many parents, however, described some positive components of reduced mobility that included fewer worries about safety and a reduction in the child’s ability to engage in some negative behaviors.

“In the last year she lost pretty much all mobility as far as being able to walk, and it was really frustrating for her... she would thrash around on the floor and just trying to walk I guess and just thrashing and crawling, and we got to the point that she was gonna hurt herself.” (FG 3)

Sleep Issues

Though some parents indicated that sleep was not a problematic symptom for their child, most parents reported that their children had sleep issues now or in past stages. Some parents identified that lack of sleep had a global impact on their child, including their behavioral issues and health.

“Whenever she doesn’t sleep at night, that sets us up for a horrible day the next day. She’s not at her best throughout the entire day, and all day I’m like ‘It’s cause she’s tired....’ She just can’t function at her best if she was up for five hours in the middle of the night.” (FG 2)

Frequent Illness, Vulnerability to Illness, and Seizures

A small number of parents reported medical symptoms that were not well-controlled. These included chronic congestion, respiratory concerns, and lung infections. Many parents reported that ear infections were problematic at some point in their child’s life but that ear tubes

provided some level of management. Some parents reported problematic seizures, which were a contributing factor for frequent hospital visits and resulted in stress and worry for families.

“He always sounds congested. He always sounds like there should be tons and tons of gunk in his lungs, but it always seems to be upper respiratory, and he’s just not strong enough anymore to cough it up.” (FG 3)

Nutrition, Feeding, and Toileting

Many of the parents described challenges with feeding and maintaining adequate nutrition for their children. The specific needs of the children changed as the disease course advanced, progressing from specific food avoidance, to inability to self-feed, to tube-feeding. While these symptoms primarily impacted the health of the affected child, some parents described an impact on the caregiver and family function, indicating a great time commitment associated with eating and toileting issues, often limiting other activities for the family.

Toileting challenges across the disease progression were also commonly described. Reported challenges included chronic loose stool or constipation, late and difficult or commonly the inability to complete toilet training, loss of bowel and bladder control, smearing of feces, and issues with diapering teenage and adult patients. Most parents reported that toileting challenges had limited impact on their child but had considerable impact on caregivers and the family. Two parents identified their child’s frustration with being able to use the toilet independently, but often being unable to make it to the toilet in time due to frequent diarrhea.

“It’s a digestive kind of stuff where she has a lot of problems with going potty, and we probably spend an hour and a half to two hours a day on the potty with her. It just takes up an enormous amount of our time. It has a big impact on our day and our ability to do other things. So, if you take into account all the time you’re feeding

her and you're having her on the potty, it's like thirty percent of the day." (FG 3)

Unmet Needs and Potential Treatment Targets

Participants agreed that the most pressing unmet treatment needs matched the many symptoms they identified under the physical health and cognitive/behavioral/psychological domains reported above, especially related to communication and behavior. Most participants were able to identify important treatment targets under each domain regardless of the extent of their child's disease progression and were emphatic about the importance of even modest treatment-related benefits on the quality of life for their children and the family. Many respondents described the importance of symptom mitigation in supporting their ability to meet their own "good parenting" goals.

"Our expectations in what we would like to get from treatments for Sanfilippo are relatively small... 'cause some of those small things have a big impact on us." (FG 3)

"You know, I'll take that [my child] can sit and enjoy doing something for three more minutes than before. I'll even take an intensive invasive medical procedure to get me six more months. I'll take any of it, and I think any of it would be good for [my child]." (FG 3)

Most parents perceived that new drug development was primarily focused on improving the cognitive abilities of a child with Sanfilippo syndrome. Parents stated that cognitive functioning was an overarching element to many of the symptoms identified as problematic, but all participants agreed that improvement in global cognitive function should not be the exclusive treatment target for Sanfilippo syndrome. Further, if a treatment became available that was not able to alter cognitive ability but would positively impact other physical aspects of the disease, this would still be a highly desired treatment option. There was overwhelming agreement that maintenance of the child's current level of function

was a highly acceptable outcome, regardless of the stage of progression of participants' children. Parents reported hoping that their children could maintain their current skill set or experience a slower rate of decline.

"... just putting a pause on the disease for six months. And then there's six months longer to live. That would be spectacular even if it is just six months ... if [my child's] cognitive functioning was like a six-month-old, but stably at six months, I would be overjoyed." (FG 2)

"I'm optimistic that one of these clinical trials... will actually prove good enough results that they'll want to push it forward... I don't care if it's not a cure. To keep him where he's at right now, that would be amazing. I would do anything for that. So that's what I'm hopeful for." (FG 3)

The concept of tolerance for risky treatments or procedures emerged during the discussion prompted by the moderator around an ideal treatment; there was strong support and willingness among most participants to "try anything" for even a modest improvement in their child's symptoms. Parent participants endorsed a desire for as broad as possible access to clinical trials and later to approved therapies. Parents of children who were older or further progressed in their disease course expressed disappointment in the age limitations for past and ongoing treatment trials. They noted that clinical trials were only available to young children with Sanfilippo syndrome, yet many children with this disorder are not diagnosed until after the age of inclusion for clinical trials.

"We applied my child for the [name of] trial, and they said no because he was two months over the cutoff... I was like 'This is so wrong in every way, shape, and form that you guys are basing this off a number.' Like, 'You guys should not be basing this off a number...'. Because for them yes, it's the measuring and everything, but it's also because their ultimate goal is a cure. Ours is quality of life." (FG 1)

Participants emphasized improving quality of life for the child, caregivers, and family as

their primary goal for new treatments. To recognize experiences when their child's needs had been met, parents were prompted to describe the "best day" that they experienced with their child in the past week. Participants identified incidents where their children engaged to a degree in fulfilling and what would be considered developmentally or age-appropriate activities, like swimming in the pool or riding amusement park rides for the first time. Some parents described instances when their children were included by and expressed themselves positively to peers. Several recounted how their children conveyed happiness in situations where they recognized something familiar and cherished, such as laughing with those close to them or pointing at a favorite cartoon character on television. In addition, several parents mentioned how their child "should have declined" based on the expected course of illness, but parents felt positive that the expected decline had not yet occurred. It is not known whether these were children who had participated in clinical trials. These parents expressed their appreciation for being able to witness their child's maintenance of valued functions.

"Even though we might be new, it's not that we don't know what [the diagnosis] really means, but we don't look at our child as terminal.... We look for things that help him, and we can be told that we're in denial all day long, and that's fine for me because I do know what the outcome is gonna be, but that's not what I'm focusing on.... What I don't like to be told is to make memories.... I don't see my life as making memories. I see it as we're living every day because that's what I do anyway. My husband will look at me, and he says, 'My child's not temporary.' And I don't think he is temporary." (FG 2)

These "best day" scenarios had conceptual overlap with the themes associated with potential treatment targets. Even given the high burden of disease, most parents expressed hope for their child's health, well-being, and life expectancy. Some participants, especially parents of younger children or of children with relatively less disease progression, expressed

optimism about new treatment options becoming available during their child's lifetime.

DISCUSSION

This study provides evidence about the significant impact Sanfilippo syndrome has on affected children and their families, and the symptomatic treatment priorities of caregivers for their children. Our results overlap with the symptom domains raised in recent FDA Listening Sessions [34, 35]; however, here we report results from an IRB-approved research methodology inclusive of a larger sample of caregivers with a focus on preferences for meaningful treatment targets with the aim of informing biopharmaceutical companies and decision-makers. Most parents identified considerable disease impact and caregiver burden associated with Sanfilippo syndrome in their children, consistent with prior reports [17–21]. Further, parents identified symptoms with high impact on their caregiving experience. When asked about perceptions of non-curative treatments, participants emphasized the importance of stopping or slowing the symptoms associated with disease progression. Studies of other severe pediatric disorders have also reported parental acceptance of treatments that, at best, maintain current function [48–50].

Symptoms relating to expressive communication, problematic behaviors, mobility, and pain were most universally identified as conferring the greatest burden and representing the most significant unmet treatment need. Participants reported that even a modest impact on valued symptoms was considered meaningful to parents given the progressive nature of Sanfilippo syndrome and the potential improvements to quality of life of the affected child and the family. In addition, parents advocated for clinical trials that assess outcomes other than, or in addition to, currently used global cognitive measures, e.g., improvements in mobility or treatments for pain management would be meaningful, even in the absence of evidence for global improvement in cognition. Additionally, parents advocated for trials that have broad inclusion criteria and allow participation of

children in more advanced stages of Sanfilippo syndrome progression, necessarily shifting focus from cognitive to other multisystem outcome measures.

Most parents expressed hopefulness related to their children's lives, which has been associated with positive coping and adaptation, considering an uncertain future [51–53]. Parents of younger children with relatively less progressed disease status expressed optimism that new treatment options would become available during their child's lifetime. Treatment-related optimism has also been described in other rare-disease parent studies [54–56].

Limitations

There are several limitations to this exploratory study. Participation in focus groups was limited to English-speaking persons living in the United States. Recruitment was conducted primarily through an advocacy group, and participants were required to attend the focus groups in person, which may have caused selection bias, especially for focus groups conducted during the 2018 International MPS Symposium, which likely required longer travel distances. As noted in the participant characteristics table, our sample comprised 92% Caucasians and 76% females. Data were not collected on income, education level, or proximity of participants to healthcare facilities. Further research incorporating a sample of participants more closely representative of the sociodemographic and geographic diversity, and comprising a wider range of caregiver roles within the Sanfilippo syndrome population, would provide important additional insight into the community's experiences and desired treatment goals. Participants' children varied in disease stages and ages among the mixed focus groups. While this approach encouraged a rich and deep exploration across the disease progression, it resulted in less specificity within the stages of Sanfilippo syndrome. Due to the low numbers of participants who reported about their children with subtype B and subtype C, we were unable to delineate the findings by subtype in this analysis. The severe communication and cognitive

impairments that occur in patients with Sanfilippo syndrome typically do not allow for accurate self-reporting, so we are limited to proxy caregiver reports. Therefore, this study focused on the caregiver experience and their interpretation of disease impact upon their children, as well as their symptom focused treatment priorities.

CONCLUSIONS

While there is a variation in symptoms and severity among children with Sanfilippo syndrome, it is evident that parents desire a treatment that eases the burden on their children and on the family. Parents can readily identify symptoms that would provide a higher quality of life if improved through a new therapy, noting that even modest benefits to those symptoms would be highly valued. Acknowledging that clinical trials in Sanfilippo syndrome have historically focused on global cognitive measures, parents in this study stressed that they place a high value on treatment outcomes targeted to narrower aspects and subsets of developmental skills, as well as a variety of non-cognitive disease manifestations. These data provide insight into parents' treatment priorities and impact of various disease manifestations that can be used to guide the selection of outcome measures in clinical trials, symptom targets for future therapeutic development, and regulatory decision-making. Subsequent research examines caregiver perspectives around treatment priorities and meaningful outcome measures.

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Compliance with Ethics Guidelines. The RTI International IRB approved STUDY0020238 under a Social/Behavioral or Non-Interventional Research protocol. The procedures used in this study adhere to the tenets of the Declaration of Helsinki. Written informed consent to participate and publish this data was obtained from all participants. No identifying information is included in the manuscript.

Data Availability. This study collected in-depth qualitative data from caregivers of children with a very rare disease, and thus our data is extremely difficult to de-identify. The

informed consent signed by our participants specifies that their data will be kept confidential and that only aggregated data and illustrative quotes will be reported. Thus, the raw data from this study will not be accessible. Requests for coding reports, however, may be sent to Cure Sanfilippo Foundation, the owner of the resulting data.

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REFERENCES

1. Gaffke L, Pierzynowska K, Piotrowska E, Wegrzyn G. How close are we to therapies for Sanfilippo disease? *Metab Brain Dis.* 2018;33(1):1–10. <https://doi.org/10.1007/s11011-017-0111-4> (PubMed PMID: 28921412).
2. Jakobkiewicz-Banecka J, Gabig-Ciminska M, Kloska A, Malinowska M, Piotrowska E, Banecka-Majkutewicz Z, et al. Glycosaminoglycans and mucopolysaccharidosis type III. *Front Biosci (Landmark Ed).* 2016;21:1393–409. <https://doi.org/10.2741/4463> (PubMed PMID: 27100513).
3. Valstar MJ, Ruijter GJ, van Diggelen OP, Poorthuis BJ, Wijburg FA. Sanfilippo syndrome: a mini-review. *J Inher Metab Dis.* 2008;31(2):240–52. <https://doi.org/10.1007/s10545-008-0838-5> (PubMed PMID: 18392742).

4. Meyer A, Kossow K, Gal A, Mühlhausen C, Ullrich K, Braulke T, et al. Scoring evaluation of the natural course of mucopolysaccharidosis type IIIA (Sanfilippo syndrome type A). *Pediatrics*. 2007;120(5):e1255–61. <https://doi.org/10.1542/peds.2007-0282> (PubMed PMID: 17938166).
5. Cleary MA, Wraith JE. Management of mucopolysaccharidosis type III. *Arch Dis Child*. 1993;69(3):403–6. <https://doi.org/10.1136/adc.69.3.403> (PubMed PMID: 8215557).
6. Andrade F, Aldámiz-Echevarría L, Larena M, Couce ML. Sanfilippo syndrome: overall review. *Pediatr Int*. 2015;57(3):331–8. <https://doi.org/10.1111/ped.12636> (PubMed PMID: 25851924).
7. van de Kamp JJ, Niermeijer MF, von Figura K, Giesberts MA. Genetic heterogeneity and clinical variability in the Sanfilippo syndrome (types A, B, and C). *Clin Genet*. 1981;20(2):152–60 (PubMed PMID: 6796310).
8. Ruijter GJ, Valstar MJ, van de Kamp JM, van der Helm RM, Durand S, van Diggelen OP, et al. Clinical and genetic spectrum of Sanfilippo type C (MPS IIC) disease in The Netherlands. *Mol Genet Metab*. 2008;93(2):104–11. <https://doi.org/10.1016/j.ymgme.2007.09.011> (PubMed PMID: 18024218).
9. Nidiffer FD, Kelly TE. Developmental and degenerative patterns associated with cognitive, behavioural and motor difficulties in the Sanfilippo syndrome: an epidemiological study. *J Ment Defic Res*. 1983;27(Pt 3):185–203 (PubMed PMID: 6415286).
10. Valstar MJ, Marchal JP, Grootenhuis M, Colland V, Wijburg FA. Cognitive development in patients with Mucopolysaccharidosis type III (Sanfilippo syndrome). *Orphanet J Rare Dis*. 2011;6:43. <https://doi.org/10.1186/1750-1172-6-43> (PubMed PMID: 21689409).
11. Cross EM, Hare DJ. Behavioural phenotypes of the mucopolysaccharide disorders: a systematic literature review of cognitive, motor, social, linguistic and behavioural presentation in the MPS disorders. *J Inherit Metab Dis*. 2013;36(2):189–200. <https://doi.org/10.1007/s10545-012-9572-0> (PubMed PMID: 23385295).
12. Cross EM, Grant S, Jones S, Bigger BW, Wraith JE, Mahon LV, et al. An investigation of the middle and late behavioural phenotypes of Mucopolysaccharidosis Type-III. *J Neurodev Disord*. 2014;6(1):46. <https://doi.org/10.1186/1866-1955-6-46> (PubMed PMID: 25657821).
13. Węgrzyn G, Jakóbkiewicz-Banecka J, Narajczyk M, Wiśniewski A, Piotrowska E, Gabig-Cimińska M, et al. Why are behaviors of children suffering from various neuronopathic types of mucopolysaccharidoses different? *Med Hypotheses*. 2010;75(6):605–9. <https://doi.org/10.1016/j.mehy.2010.07.044> (PubMed PMID: 20732748).
14. Colville GA, Watters JP, Yule W, Bax M. Sleep problems in children with Sanfilippo syndrome. *Dev Med Child Neurol*. 1996;38(6):538–44. <https://doi.org/10.1111/j.1469-8749.1996.tb12114.x> (PubMed PMID: 8647333).
15. Fraser J, Gason AA, Wraith JE, Delatycki MB. Sleep disturbance in Sanfilippo syndrome: a parental questionnaire study. *Arch Dis Child*. 2005;90(12):1239–42. <https://doi.org/10.1136/adc.2004.065482> (PubMed PMID: 16301549).
16. Mariotti P, Della Marca G, Iuvone L, Vernacotola S, Ricci R, Mennuni GF, et al. Sleep disorders in Sanfilippo syndrome: a polygraphic study. *Clin Electroencephalogr*. 2003;34(1):18–22 (PubMed PMID: 12515448).
17. Somanadhan S, Larkin PJ. Parents' experiences of living with, and caring for children, adolescents and young adults with Mucopolysaccharidosis (MPS). *Orphanet J Rare Dis*. 2016;11(1):138. <https://doi.org/10.1186/s13023-016-0521-0> (PubMed PMID: 27724940).
18. Malcolm C, Hain R, Gibson F, Adams S, Anderson G, Forbat L. Challenging symptoms in children with rare life-limiting conditions: findings from a prospective diary and interview study with families. *Acta Paediatr*. 2012;101(9):985–92. <https://doi.org/10.1111/j.1651-2227.2012.02680.x> (PubMed PMID: 22452449).
19. Grant S, Cross E, Wraith JE, Jones S, Mahon L, Lomax M, et al. Parental social support, coping strategies, resilience factors, stress, anxiety and depression levels in parents of children with MPS III (Sanfilippo syndrome) or children with intellectual disabilities (ID). *J Inherit Metab Dis*. 2013;36(2):281–91. <https://doi.org/10.1007/s10545-012-9558-y> (PubMed PMID: 23151683).
20. Shapiro E, Lourenço CM, Mungan NO, Muschol N, O'Neill C, Vijayaraghavan S. Analysis of the caregiver burden associated with Sanfilippo syndrome type B: panel recommendations based on qualitative and quantitative data. *Orphanet J Rare Dis*. 2019;14(1):168. <https://doi.org/10.1186/s13023-019-1150-1>. PubMed PMID.
21. Conijn T, Nijmeijer SCM, van Oers HA, Wijburg FA, Haverman L. Psychosocial functioning in parents of MPS III patients. *JIMD Rep*. 2019;44:33–41. https://doi.org/10.1007/8904_2018_119 (PubMed PMID: 29980992).

22. Giugliani R, Federhen A, Vairo F, Vanzella C, Pasqualim G, da Silva LM, et al. Emerging drugs for the treatment of mucopolysaccharidoses. *Expert Opin Emerg Drugs*. 2016;21(1):9–26. <https://doi.org/10.1517/14728214.2016.1123690> (PubMed PMID: 26751109).
23. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT03784287, A treatment extension study of mucopolysaccharidosis Type IIIB. 2018 [cited 2020 November 11]. <https://ClinicalTrials.gov/show/NCT03784287>.
24. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT04018755, Open-label Study of Anakinra in MPS III. 2019 [cited 2020 November 11]. <https://ClinicalTrials.gov/show/NCT04018755>.
25. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT03811028, A study to assess the safety, tolerability, and efficacy of long-term sobi003 treatment in pediatric MPS IIIA patients. 2019 [cited 2020 November 11]. <https://ClinicalTrials.gov/show/NCT03811028>.
26. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT03315182, Gene transfer clinical trial for mucopolysaccharidosis (MPS) IIIB. 2017 [cited 2020 November 11]. <https://ClinicalTrials.gov/show/NCT03315182>.
27. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT04088734, Gene transfer study of ABO-102 in patients with middle and advanced phases of MPS IIIA disease. 2019 [cited 2020 November 11]. <https://clinicaltrials.gov/ct2/show/NCT04088734>.
28. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT02716246, Phase I/II gene transfer clinical trial of scAAV9.U1a.hSGSH. 2016 [cited 2020 November 11]. <https://ClinicalTrials.gov/show/NCT02716246>.
29. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT01299727, Extension of Study HGT-SAN-055 evaluating administration of rhHNS in patients with Sanfilippo syndrome Type A (MPS IIIA). 2011 [cited 2020 November 11]. <https://ClinicalTrials.gov/show/NCT01299727>.
30. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT02350816, An extension study to determine safety and efficacy for pediatric patients with MPS Type IIIA disease who participated in Study HGT-SAN-093. 2015 [cited 2020 November 11]. <https://ClinicalTrials.gov/show/NCT02350816>.
31. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT02618512, A open label study in previously studied, SBC-103 treatment naïve MPS IIIB subjects to investigate the safety, pharmacokinetics, and pharmacodynamics/efficacy of SBC-103 administered intravenously. 2015 [cited 2020 November 11]. <https://ClinicalTrials.gov/show/NCT02618512>.
32. European Medicines Agency. The patients voice in the evaluation of medicines. 2013. https://www.ema.europa.eu/en/documents/report/report-works-hop-patients-voice-evaluation-medicines_en.pdf. Accessed 18 Oct 2019.
33. United States Public Law 114-255 (Pub.L. 114–255). An Act to accelerate the discovery, development, and delivery of 21st century cures, and for other purposes. 2016.
34. U.S. Food and Drug Administration. Sanfilippo syndrome (pediatric) - FDA-requested Listening Session. 2019. <https://www.fda.gov/media/133550/download>. Accessed 6 Dec 2019.
35. U.S. Food and Drug Administration. Sanfilippo Syndrome - FDA-requested Listening Session. 2019. <https://www.fda.gov/media/133549/download>. Accessed 6 Dec 2019.
36. U.S. Department of Health and Human Services Food and Drug Administration. Developing and Submitting Proposed Draft Guidance Relating to Patient Experience Data Guidance for Industry and Other Stakeholders. 2018. <https://www.fda.gov/media/119542/download>. Accessed 6 February 2019.
37. O'Neill C, Mansfield C, Drake E, Coulter J, Peay HL. Parent prioritization of meaningful treatment targets for Sanfilippo syndrome. *Mol Genet Metab*. 2020;129(2):S121. <https://doi.org/10.1016/j.ymgme.2019.11.315>.
38. Neuman LW. *Social research methods: qualitative and quantitative approaches*. 7th ed. Boston: Allyn and Bacon; 2011.
39. Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol*. 2006;3:77–101.
40. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. *Qual Health Res*. 2005;15(9):1277–88. <https://doi.org/10.1177/1049732305276687> (PubMed PMID: 16204405).
41. QSR International Pty Ltd. (2018) NVivo (version 12). <https://www.qsrinternational.com/nvivo-qualitative-data-analysis-software/home>.

42. Chenail RJ. Conducting qualitative data analysis: qualitative data analysis as a metaphoric process. *Qual Rep.* 2012;17:248–53.
43. Erlandson DAHE, Skipper BL, Allen SD. *Doing naturalistic inquiry: A guide to methods.* Thousand Oaks: Sage Publications; 1993.
44. Marshall MN. Improving quality in general practice: qualitative case study of barriers faced by health authorities. *BMJ.* 1999;319(7203):164–7. <https://doi.org/10.1136/bmj.319.7203.164> (PubMed PMID: 10406756).
45. Hauer J, Houtrow AJ, Section On H, Palliative Medicine COCWD. Pain assessment and treatment in children with significant impairment of the central nervous system. *Pediatrics.* 2017. <https://doi.org/10.1542/peds.2017-1002> (PubMed PMID: 28562301).
46. Thompson VN, Morse BL, Peters AB. Pain assessment approaches for students with intellectual disability. *NASN Sch Nurse.* 2020. <https://doi.org/10.1177/1942602X20915819> (PubMed PMID: 32356491).
47. Barbi E, Badina L, Massaro M, Pisciotta G, Ventura A. Paediatricians' attitudes toward pain in children with severe cognitive impairment. A regional survey. *Pediatr Med Chir.* 2014;36(4):94. <https://doi.org/10.4081/pmc.2014.94> (PubMed PMID: 25573710).
48. McGraw S, Qian Y, Henne J, Jarecki J, Hobby K, Yeh WS. A qualitative study of perceptions of meaningful change in spinal muscular atrophy. *BMC Neurol.* 2017;17(1):68. <https://doi.org/10.1186/s12883-017-0853-y> (PubMed PMID: 28376816).
49. Rouault F, Christie-Brown V, Broekgaarden R, Gusset N, Henderson D, Marczuk P, et al. Disease impact on general well-being and therapeutic expectations of European Type II and Type III spinal muscular atrophy patients. *Neuromuscul Disord.* 2017;27(5):428–38. <https://doi.org/10.1016/j.nmd.2017.01.018> (PubMed PMID: 28237437).
50. Peay HL, Hollin I, Fischer R, Bridges JF. A community-engaged approach to quantifying caregiver preferences for the benefits and risks of emerging therapies for Duchenne muscular dystrophy. *Clin Ther.* 2014;36(5):624–37. <https://doi.org/10.1016/j.clinthera.2014.04.011> (PubMed PMID: 24852596).
51. Herth KA. The relationship between level of hope and level of coping response and other variables in patients with cancer. *Oncol Nurs Forum.* 1989;16(1):67–72 (PubMed PMID: 2911529).
52. Felder BE. Hope and coping in patients with cancer diagnoses. *Cancer Nurs.* 2004;27(4):320–4. <https://doi.org/10.1097/00002820-200407000-00009> (PubMed PMID: 15292728).
53. Bell M, Biesecker BB, Bodurtha J, Peay HL. Uncertainty, hope, and coping efficacy among mothers of children with Duchenne/Becker muscular dystrophy. *Clin Genet.* 2019;95(6):677–83. <https://doi.org/10.1111/cge.13528> (PubMed PMID: 30847900).
54. Mack JW, Cook EF, Wolfe J, Grier HE, Cleary PD, Weeks JC. Understanding of prognosis among parents of children with cancer: parental optimism and the parent-physician interaction. *J Clin Oncol.* 2007;25(11):1357–62. <https://doi.org/10.1200/jco.2006.08.3170> (PubMed PMID: 17416854).
55. Peay HL, Scharff H, Tibben A, Wilfond B, Bowie J, Johnson J, et al. "Watching time tick by...": Decision making for Duchenne muscular dystrophy trials. *Contemp Clin Trials.* 2016;46:1–6. <https://doi.org/10.1016/j.cct.2015.11.006> (PubMed PMID: 26546066).
56. Hinton D, Kirk S. Living with uncertainty and hope: a qualitative study exploring parents' experiences of living with childhood multiple sclerosis. *Chronic Illn.* 2017;13(2):88–99. <https://doi.org/10.1177/1742395316664959> (PubMed PMID: 27539955).