

## Title: Niemann-Pick Type C Patient and Caregiver Voices: Externally-led, Patient-Focused Drug Development Meeting

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Niemann-Pick Type C Patient and Caregiver Voices:  
*Externally-led, Patient-Focused Drug Development Meeting*

March 18, 2019  
Hyattsville, Maryland



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## REPORT SUMMARY



Niemann-Pick Type C (NPC) disease is an ultra-rare, progressive, and fatal neurovisceral disorder with highly heterogeneous systemic and neurological symptoms and unpredictable progression. Caused by mutations in one of two genes (NPC1 and NPC2), the disease is inherited in an autosomal recessive manner, meaning that both parents must carry mutations in the same gene. The incidence of NPC is estimated to be about 1 case per 100,000 live births, **(1)** although prevalence may actually be higher due to misdiagnosis. **(2)** Despite the rarity of the disease, more than 50 families attended or participated via webcast in a meeting held on March 18, 2019 in Hyattsville, Maryland to gather patient voices on the experience and burden of disease and its treatment and share their perspectives with representatives from the U.S. Food and Drug Administration (FDA).

The meeting was organized under the aegis of the FDA's externally-led Patient-Focused Drug Development (PFDD) Initiative and was spearheaded by the Ara Parseghian Medical Research Fund, joined by partner organizations Dana's Angels Research Trust, Firefly Fund, Johnathan's Dreams, Hide & Seek Foundation, Hope for Marian, National Niemann-Pick Disease Foundation, and Niemann-Pick Canada. The PFDD program was initiated by the FDA and Congress in 2012 to "more systematically obtain the patient perspective on specific diseases and their treatment." It was designed to learn from patients and families how they feel, function, and survive with these diseases to aid drug developers and the FDA in decision making about therapy development and approval.

Prior to the NPC PFDD meeting, 83 people in the United States completed a survey about their experiences with the disease and its treatment. Survey respondents comprised individuals with NPC as well as both current and former caregivers. The data from this survey was used to shape the meeting and develop discussion questions designed to collect information helpful to other families living with NPC as well as drug developers and regulators.

Following welcome remarks and a brief description of the meeting agenda, an introductory presentation by a representative of the FDA Division of Gastroenterology and Inborn Errors Products described the FDA's approach to rare disease drug development and the value the agency puts on the patient voice. A pediatric neurologist with extensive experience treating people with NPC then provided an overview of the disease and current treatments.

To supplement the data collected in the survey, three panels of NPC patients and representatives were organized around three discussion topics. After each panelist gave a brief presentation, audience members and those participating by webcast were invited to respond to a series of polling questions similar to those asked in the survey. Polling was followed by a facilitated discussion among audience members.

The first panel, composed of individuals or caregivers of individuals with late infantile- and juvenile-onset disease, discussed symptoms of NPC and daily impacts that matter most to them. The second panel, also composed of individuals and caregivers of individuals with late infantile- and juvenile-onset disease, discussed current approaches to treating NPC and their desires for future treatments. The third panel, composed of individuals and caregivers of individuals with early infantile- and adult-onset disease, discussed symptoms of NPC and daily impacts that matter most.

The meeting was broadcast to the public from a dedicated website set up for the initiative. The full recording can be viewed at this link: [niemannpickc-pfdd.com/stream/](https://niemannpickc-pfdd.com/stream/).

The pre-meeting survey data combined with polling data and remarks from panelists and audience participants provided the content of this “Voice of the Patient” report. Key themes emerging from these data are summarized below and explored in greater detail in the report.

**NPC is a devastating disease with substantial impact on all aspects of a patient’s and family’s life.**

- Individuals with NPC may be unable to perform personal care tasks or participate in physical and social activities, resulting in a loss of independence and increased isolation from peers.
- Even on the best days, NPC symptoms have a moderately high negative impact on activities of daily living.
- NPC is ultra-rare, highly variable, and heterogeneous in presentation, resulting in diagnostic and trial design challenges.
- NPC can present at any stage of life with a diverse group of symptoms and variable speed and patterns of progression.
- Many patients present an enlarged spleen, jaundice, and/or liver issues or failure at birth, but these symptoms may not be recognized as signs of NPC.
- Eye movement problems are often one of the earliest symptoms of NPC.
- Neurological involvement results in ambulation and walking difficulties, cognitive impairment, swallowing difficulties, vertical supranuclear gaze palsy (VSGP), seizures, and cataplexy.
- Visceral organs such as the spleen, liver, kidneys and lungs may be damaged throughout the course of disease.
- Patients can be diagnosed before any visible signs or symptoms of the disease are apparent by being genetically screened through Whole Exome Sequencing (WES), which often occurs only after the disease has been confirmed in a sibling.
- Adolescent- and adult-onset NPC onset can include mental illnesses such as psychosis and bipolar disorder, which can be among the most problematic symptoms of the disease.
- The mainstay of treatment is symptomatic and many treatments are associated with substantial adverse effects.
- No disease-modifying treatments have been approved in the United States for the treatment of NPC.
- The varied nature of NPC symptoms and disease progression presents challenges for treatment.
- Assistive devices such as wheelchairs, walkers, braces, gastrostomy tubes, and pulmonary vests, as well as multidisciplinary therapy are often required to maximize function.
- Investigational drug treatments provided through clinical trials and expanded access programs appear beneficial for many patients but may have highly burdensome protocols.
- It is unclear whether adverse events associated with treatment are a result of the treatment itself or the symptom being treated (e.g., seizures).

**People with NPC and their families are eager to participate in research and drug development and are willing to take substantial risk in the search for new treatments.**

- Patients and families most desire new treatments for neurological symptoms and improved quality of life even if they do not extend life span. Recognizing the heterogeneity of disease progression and symptoms, NPC patients and families emphasize the need for multiple therapeutic options so that treatment approaches can be tailored to meet individual patient needs.



## INTRODUCTION



On March 18, 2019, the Niemann-Pick Type C (NPC) disease community came together for a patient-focused drug development (PFDD) meeting to inform members of the U.S. Food and Drug Administration (FDA) and drug developers about the experience of living with NPC and what matters most to patients and families with regard to treatment. The meeting followed the template established by the FDA for externally-led PFDD meetings and was also attended by many FDA representatives. Over 50 NPC families attended the meeting and others joined by webcast.

Prior to the meeting, a survey was distributed through several advocacy organizations, social media sites, and word of mouth to gather input from diverse members of the NPC community. Data from the survey, combined with the testimony of meeting participants, are compiled in this report to provide a glimpse into the challenges and burdens faced by individuals and families affected by this devastating disease.

### Overview of Niemann-Pick Type C disease and its management

NPC is an ultra-rare (meaning it affects fewer than 2,000 individuals in the U.S.), progressive, and fatal neurovisceral disorder. One of a group of diseases called lysosomal storage disorders, NPC is caused by mutations in either the NPC1 (95% of cases) or NPC2 gene. The proteins encoded by these genes are involved in the trafficking of lipids and other large molecules within cells. **(3)** More than 400 mutations have been identified in NPC1 **(4)** and more than 20 have been identified in NPC2 (Zampieri 2014). NPC is inherited in an autosomal recessive manner, meaning that both parents must carry a mutation. The mutations result in intracellular accumulation of complex lipid compounds, causing an inflammatory response and increased cell death in multiple organs and tissues across the lifespan. The disease can present at any stage of life and can strike unexpectedly with highly variable and insidious symptomatology.

NPC is often categorized by age of neurological onset: early infantile (onset before age 2), late infantile (onset between ages 2 and 6), juvenile (onset between ages 6 and 15), and adult onset (onset after age 15), although the expression and progressions of the disease is unique for each individual. **(5)** In general, earlier onset of disease is associated with more rapid progression and greater severity.

Disease onset during fetal life and the perinatal period typically involves the liver, spleen, and lungs. Enlargement of the spleen may be the only manifestation of disease at this stage and may regress and recur over time. Some infants with spleen enlargement at birth do not develop other symptoms until later in childhood. For other infants, the disease progresses more rapidly and presents as a predominantly neurological disease with symptoms reflecting the progressive dysfunction and loss of specific neurons throughout the central nervous system. Thus, infants may present with low muscle tone and developmental delays.

Spleen enlargement may also appear later in infancy or in early childhood. By around age 3, most children with NPC present with vertical supranuclear gaze palsy, which is highly characteristic of the disorder. Young children may also appear clumsy, which can progress to clear ataxia. As they get older, children may show problems with gait, speech delay or articulation problems, and gelastic cataplexy, the sudden loss of muscle tone that is evoked by strong emotions. Onset later in childhood may present as difficulties in school stemming in part from inattention. Many children develop seizures. Onset

during adolescence and young adulthood may present with cognitive and psychiatric problems. Sleep dysfunction is also common among people with NPC.

The high variability and lack of specificity of most signs and symptoms of NPC, combined with the fact that most clinicians will have little or no experience with the disease, leads to substantial diagnostic delays, misdiagnoses, delayed intervention, and high levels of frustration and stress among families and caregivers. The average delay in diagnosis is about five years according to several care centers, by which time the nervous system may be severely damaged. There is a growing effort in the community to promote newborn screening for NPC, which holds the promise for earlier diagnosis in future patients.

There is currently no cure for NPC although research on the disease is fairly robust and several therapies are in development. **(6)** Based on data collected from the survey for this initiative, the vast majority of current NPC patients are currently on or have previously used one or more treatments or experimental therapies to manage their disease. The drug miglustat has been approved as a disease-modifying drug for the treatment of neurological symptoms of NPC in Europe, Canada, and Japan, but has not yet been approved for NPC by the FDA.<sup>1</sup> Miglustat is approved in the United States for Gaucher disease (another lysosomal storage disease) and many NPC patients have gained access to the drug either through open-label extension of a clinical trial or off-label prescription. Multiple distinct forms of another class of drugs called cyclodextrins are currently being tested in clinical trials. These drugs have shown promise in slowing disease progression. **(7)** Other drugs being used by patients or in development for NPC or related morbidities include anti-cataplexy, anti-narcolepsy, anti-seizure, anti-depressant, and anti-psychotic medications, neurosteroids, sleep medications, medications to improve muscle tone, histone deacetylase inhibitors, ariclomol, and liver X receptor (LXR) and pregnane X receptor (PXR) agonists. The mainstay of management, however, is symptom management through multi-disciplinary therapy to address medical, physical, and psychological aspects of the disease.

Only about 500 people worldwide and about 100 in the United States are known to have the disease, although with an estimated incidence of 1 in 100,000 live births, **(1)** the actual number may be as high as 2,000 due to misdiagnosis. The rarity of the disease limits the number of potential participants for clinical studies and diagnostic delays mean few individuals are identified in early disease stages when treatment may provide increased benefit. Clinical studies are further complicated by an incomplete understanding of disease mechanisms and clinical heterogeneity. Attaining long-term natural history data of the disease could help illuminate these elements, but such data on the current population may also be influenced by the high level of exposure to approved and experimental therapies among the population. In addition, there are no validated biomarkers or surrogate clinical intermediate endpoints and there is a need for more clinically meaningful outcome measures.



### Meeting format and desired outcomes

The NPC PFDD meeting was designed to gather the patient perspective on burdens and treatments and how they influence patients' lives; and to consider different ways to capture and measure the progression of disease in patients.

Prior to the meeting, a survey was shared with people who have NPC and their caregivers through the organizers' or other advocacy organizations' websites, other internet and social media sites, and by word-of-mouth from healthcare providers, friends, and family members. The survey informed the meeting content and the selection of participants. Meeting panelists were selected to represent diverse perspectives and experiences across the lifespan of people with NPC.

The meeting was held in Hyattsville, Maryland on March 18, 2019. This location enabled participation and observation by FDA representatives. Over 50 NPC families attended the meeting and many others joined by webcast. They shared their experiences to give the FDA insight into what it is like to live with NPC, the complexity and variability of symptoms and progression, how they manage NPC, and what they desire in new treatments

Timothy R. Franson, M.D. served as moderator. Dr. Franson is chief medical officer at the consulting firm Yourencore, Inc. Previously he worked in global regulatory affairs for many years at Eli Lilly & Co. Opening remarks were delivered by Sean Kassen, PhD, director of the Ara Parseghian Medical Research Fund at the University of Notre Dame. The FDA's role in the drug development process and the importance they place on incorporating the patient voice was described by Dragos Roman, M.D., acting director of the Division of Gastroenterology and Inborn Errors Products at the FDA's Center for Drug Evaluation and Research (CDER). Marc C. Patterson, M.D., professor of neurology, pediatrics, and medical genetics at the Mayo Clinic Children's Center in Rochester, Minnesota then presented an overview of Niemann-Pick Type C disease and current treatments.

### Three sessions focusing on specific discussion topics followed these introductory presentations:

- Session 1 – Symptoms of NPC disease and daily impacts that matter most to patients with late infantile- or juvenile-onset NPC and their caregivers.
- Session 2 – Current approaches to treating NPC in people with late infantile- or juvenile-onset disease.
- Session 3 - Symptoms of NPC disease and daily impacts that matter most to patients with late infantile- or juvenile-onset NPC and their caregivers.

In each session, a panel of individuals with NPC disease and/or current or former caregivers of people with the disease presented brief summaries of their experiences. Panelists were selected to represent the broad spectrum and diverse experiences of living with NPC disease. Meeting attendees then responded to several polling questions similar to those asked in the survey and then participated in a moderated discussion which allowed them to share their own perspectives and experiences. An open comment period allowed participants to discuss topics not previously covered.

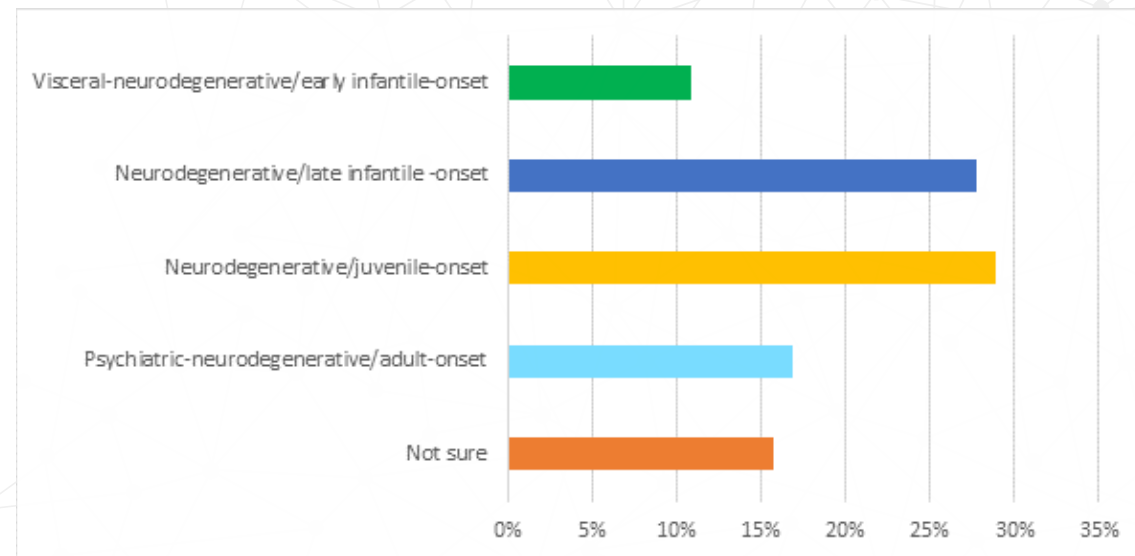


### Demographics of survey respondents

Eighty-three individuals responded to the pre-meeting survey. The vast majority of survey respondents were current or former caregivers. Most were White, non-Hispanic or Latino and 53 percent were male.

## TOPIC 1: Symptoms of Niemann-Pick Type C disease and daily impacts that matter most to patients and caregivers

Figure 1: Types of Niemann-Pick Type C as reported by survey respondents



### Disease characteristics of survey respondents

As shown in Figure 1, survey respondents represented all categories of NPC: Visceral-neurodegenerative/early infantile form (10.8%), neurodegenerative/late infantile form (27.7%), neurodegenerative/juvenile form (28.9%), psychiatric-neurodegenerative/adult form (16.9%). 15.7% were not sure.

The age at which symptoms of NPC first appeared ranged from less than 2 years (31.7%), 2-5 years (23.2%), 6-15 years (28.0%), 16-29 years (14.6%), and 30 years or older (2.4%). Neurological symptoms including developmental delays, ataxia, and vertical gaze palsy first appeared in 20.2% of infants under age 2, 36.7% of children age 2-5, 27.8% of children age 6-15, 12.7% of adolescents and young adults age 16-29, and 2.5% of adults 30 years or older.



**Table 1. Symptoms that have the greatest impact on patients' and caregivers' daily life**

Symptom	Percent endorsing symptom as having greatest impact	
	On patient's daily life	On caregiver's daily life
Ambulation/walking difficulties	57.8	67.5
Cognitive impairment	57.8	53.2
Swallowing difficulty	43.4	37.7
Speech problems	33.7	29.9
Seizures	28.9	31.2
Fine motor skill impact	25.3	24.7
Respiratory disease/breathing problems	16.9	24.7
Hearing problems	13.2	13.0
Vertical gaze palsy/eye movement issues	9.6	9.1
Liver disease/failure	6.0	3.9

**Symptoms that matter most and impact on daily life**

The survey asked respondents to indicate which symptoms have the most significant impact on the patient's and caregiver's daily life. Respondents were allowed to choose up to three. Symptoms that had the most significant impact on the caregivers' lives followed a similar pattern as those having impact on patients' life, with ambulation and walking difficulties having a somewhat greater impact on caregivers' lives. Table 1 summarizes the responses to these questions.

Comments from meeting participants powerfully illustrate the far-reaching impact of disease symptoms on people with NPC and their families, including symptoms not captured by survey data. Each person's story is unique and the symptoms that most affect their lives also vary from one person to another and across the stages and ages of onset of the disease:

**Ambulation/walking difficulties**

Problems with ambulation affect the ability of children with NPC to participate in many of the social and physical activities enjoyed by their peers and may limit their independence. As illustrated in the testimonies below, ambulation problems typically combine with other motor, physical, cognitive, and social difficulties.

The father of a 16-year-old boy whose first sign of NPC was impaired coordination at about age 8 said: *"Less than one year after ataxia first appeared, his condition had deteriorated markedly. His gait became staggered, his handwriting reverted to kindergarten level, and the ataxia became more pronounced. Simple activities such as brushing teeth, or shampooing hair, became difficult tasks."*

The mother of a two-year-old with NPC said: *"NPC gave him poor gait and low muscle tone, so he's unable to climb, go up the stairs or cross the bridge alone. There are many tasks in the home that he requires help with, such as dressing himself, opening doors, getting toys, getting into bed, getting on the couch, going up and down stairs and sitting at the table still requires a booster chair. He is in constant need of assistance and being almost three means he wants his independence. The negative impact of his symptoms affect us on a daily basis. On his best days, he's able to play and interact with other children on his own and with our help, but on his worst days, he is unable to play with others, because he can't keep up or his walker isn't allowed and being only two, he doesn't understand why. Seeing his sweet, disappointed, and sad face just breaks my heart."*

After a normal, active childhood, the life of a young woman with adolescent-onset NPC dramatically changed when she was in junior high. *"I was having a hard time with a lot of my schoolwork... I still participated in sports ... but I had a hard time with my balance and coordination. I remember always being tired. I still had some close friends but it wasn't like it had been in the past... I was less talkative and engaged."*

**Cognitive impairment**

For many individuals with NPC, cognitive symptoms have the most negative impact on their lives and the lives of their families and caregivers.

The father of a 16-year-old boy whose first sign of NPC was impaired coordination at about age 8 said: *"Cognitively, he deteriorated as well. While his reading fluency was above grade level, his reading comprehension was atrocious."*

The mother of a girl with NPC said cognitive impairment impacts her life the most. *"One minute she may understand what we were saying, and then the next minute, it's like a completely different child is taking over. That's what is hardest for us, and the dementia."*

Another mother said of her son, *"Sometimes ... you can't understand him, you can't reason with him. He doesn't understand abstract thinking, that kind of thing."*

The mother of a 7-year-old diagnosed at four months of age said *"On her best days, she won't be able to remember most of her friends' names and on her worst days, NPC will keep her from remembering the name of family and close friends."*

**Swallowing problems**

Swallowing difficulties and the resulting problems associated with feeding and choking emerged as one of the most significant and life-threatening problems for people with NPC. In addition to creating challenges for day-to-day eating and drinking, swallowing difficulties significantly increase NPC patients' risk of aspiration pneumonia.

A mother of three children with NPC said of one daughter: *“A feeding tube had been inserted four months before she died [at age 10 ½], but it was probably too late to offer her the nutrition she needed to stay strong. She hated the feeding tube, pulling it out several times before she died of pneumonia.”*

The father of a 16-year-old boy diagnosed at age 11 added that even when swallowing issues appear to resolve, people with NPC may be affected by silent aspiration. *“When he drank and ate, he usually coughed and choked and now he doesn’t anymore. We’ve been treating him for six years. About a year ago, we thought he was better with that, and we found out with silent aspiration, he just lost the ability to know he’s choking and food’s going down the wrong way.”*

The mother of a daughter with NPC said: *“We are constantly living in fear of choking from not only eating the food but also just choking on saliva at night when she’s sleeping.”*

The mother of a woman with adult-onset NPC who recently passed away said (speaking as her daughter): *“I was having problems swallowing. My list of safe foods got smaller and smaller until it consisted of pasta, tuna salad, and egg salad. Eating outside our home was very difficult. All liquids had to be thickened with a special gel.”*

### **Seizures and cataplexy**

While less than one third of survey respondents ranked seizures as having the greatest impact on their lives, seizures were mentioned frequently at the meeting because of the severity of impact on daily life and independence, the adverse events associated with seizure medication, and their life-threatening potential. Cataplexy was often mentioned in association with seizures.

The mother of three children with NPC said: *“All three kids also had seizures. They started with a small staring episode, then petit mals then eventually grand mals. They also each experienced cataplexy that if you made them laugh, although it was such a beautiful sight and sound, they would lose all tone and control in their trunk and would face plant onto whatever was in front of them... Once the seizures started, we were never able to control them enough to stop them altogether, even with frequent med changes. So they became our normal.”*

Another mother who also had lost three children to NPC recalled how her son died days before his tenth birthday from a seizure: *“He had started having seizures about nine months before, but the medications never totally controlled the episodes. A seizure led to his suffocation early one morning in his bed.”*

A father of two children with NPC said his son, who had an occasionally enlarged spleen and was diagnosed at age 5, started treatment and thrived until age 14, but then started having multiple seizures per day, gait, balance, and swallowing issues. *“He cannot be left alone, cannot move around the house or anywhere else without someone by his side.”*

The father of a 19-year-old who was jaundiced at birth, misdiagnosed with neonatal hepatitis, and diagnosed with NPC at age 6 said: *“He began having seizures at the age of 12. The seizures increased to having multiple a day. Our neurologist’s answer was to give him more anti-seizure medication, which has made him more lethargic. Because of the seizures, it is very difficult to lead a semi-normal life. We do not ever leave him unattended. Not the life that a 19-year old wants. He has a nurse with him and an aide with him at school every day. He has never showered by himself. And now, when he goes to the bathroom, someone always has to go with him. Even with someone with him at all times, he can still have a seizure and fall.”*

The mother of a 22-year-old diagnosed at age 15 after a 10-year diagnostic odyssey said that the year after diagnosis, *“The dreaded grand mal seizures started... Over the next year and a half, uncontrolled seizures and multiple medications changed her life drastically. My sweet 16-year-old daughter started wearing diapers, using a walker and lost much of her ability to speak and swallow. At 17, she had a feeding tube placed, and with a ketogenic diet and proper medications, we were able to obtain seizure control. But much damage had already been done.”*

### **Loss of fine motor skills**

Like the loss of mobility, the loss of fine motor skills makes daily activities and socialization challenging for people with NPC.

For one woman with late-onset NPC disease, *“tremors got worse and worse until I couldn’t hold anything. Eventually, I couldn’t even feed myself. That was embarrassing. All these limitations made my world smaller and smaller. Going out to eat was more challenging than fun. I couldn’t go to the movies because I couldn’t keep my head raised to see the screen, and my brain didn’t understand the story anyway... I was completely dependent on other people for every part of daily life, getting dressed, brushing my teeth, everything.”*

### **Respiratory difficulties**

Ultimately, what often leads to the death of individuals with NPC are the complications of pneumonia, brought on by damage to the lungs, difficulty swallowing, and lack of ambulation, which reduce the ability to clear the lungs. Swallowing difficulties were described earlier; this section focuses on lung-related symptoms related to reduced lung capacity. It is worth noting, however, that the two types of symptoms may be connected, particularly as swallowing difficulties lead to risk of aspiration pneumonia.

One mother of three children with NPC said of one daughter, *“She struggled with pneumonia for several years...”* Another daughter was slower to show symptoms and lived the longest of the three children before dying at 16 ½. *“Maybe she lived to an older age than her siblings because we worked hard to maintain her lung capacity with breathing treatments several times a day, even when she wasn’t suffering from pneumonia. Or maybe it was the nutrition through a feeding tube that was inserted when she turned 13. Yet in the end, she too would succumb to pneumonia.”*

A father of two children with NPC said of his daughter: *“The last five years were the toughest with multiple pneumonias, long stays in the hospital, eventually needing a tracheotomy and a ventilator to breathe until... during a seemingly good period just before her 20th birthday, suddenly Dana’s liver failed and she was gone.”*

The mother a 22-year-old with NPC said, *“Her lungs are her most constant struggle. The vest, suctioning, cough assist, oxygen and oxygen, monitor are necessary to keep her out of the hospital.”*

**Vertical gaze palsy**

Vertical gaze palsy was often mentioned as the sign that alerted clinicians to the possibility that a person showing other non-specific symptoms of neurological disease might have NPC, yet it was infrequently mentioned as having substantial impact on a person’s life. Said one mother of her son, *“He couldn’t quite look me in the eye.”*

**Fatigue, sadness, depression**

The multiple motor and cognitive difficulties experienced by individuals with NPC, combined with sleep dysfunction, lead many affected individuals to struggle with fatigue. As they move into adolescence and young adulthood, loss of hope and sadness may add to this challenge. These experiences are also linked with feelings of social isolation that many patients with NPC experience.

The mother of a girl diagnosed at age 9 said: *“She often slept more, which I believe was partly due to medicines, fatigue from a mentally and physically draining of her energy to get through each day’s activities. And a lot of depression. She managed to tell me once that she was sad that she could not do anything anymore, and that her hopes and dreams were not going to come true.”*

A young woman who was diagnosed with NPC at age 15 spoke about how the disease impacted her ability to socialize: *“Before I had any symptoms from NPC, my life was normal. I enjoyed grade school, I had a great group of friends. I spent many nights at sleepovers, birthday parties, or just hanging out with my friends. I played soccer, basketball, and tennis. I was constantly active. ... At that time in my life I remember always being tired. I still had some close friends but it wasn’t like it had been in the past. My family knows that I was less talkative and engaged, this is when my parents became concerned and I started seeing doctors.”*

**Psychiatric problems**

As noted in the introduction, among people with late onset Niemann-Pick Type C disease, psychiatric problems predominate and often lead to delayed diagnosis.



The mother of a woman who recently died at age 33 said that in her daughter’s junior year of high school, her *“life fell apart... thoughts and emotions became frightening, [she] cried all the time, thought bad people were after us, lived in constant fear. Doctors used the words bipolar, psychotic, and schizoaffective. Medication did not keep her stable.”* When she turned 24, her cognitive abilities started to decline. She *“couldn’t grasp higher-level thinking, had no sense of time, could no longer read or understand content, couldn’t carry out instructions given to her five minutes before.”* At age 26 she was diagnosed with Niemann-Pick Type C.

Another mother of two sons with adult-onset NPC said, for both of them: *“their very first symptoms was psychosis. One son moved to other neurological symptoms with ataxia and gait and all of that, but my other son, really to this date has much fewer symptoms but has a very severe psychosis, which we’ve just come off of four months of dealing with. And that impact to the family is extremely, extremely stressful, financially stressful, emotionally stressful...”*

**Activities of daily living that are most impacted by NPC symptoms**

The survey also asked what activities of daily living (ADLs) are most impacted by NPC symptoms. Respondents could choose as many as necessary. The ADLs most frequently selected were personal care such as dressing, bathing, toileting (72%); exercise or participation in sports/physical activities (68.3%); school or work performance (63.4%); eating/drinking (61.0%); social activities (61.0%). Less frequently chosen were household chores or activities (43.9%); travel (34.2%); and schoolwork or performance (1.2%).

Survey respondents were also asked to rank using a scale of 1-5 (with 5 being the greatest negative impact) how much disease symptoms negatively impacts their life on the best days and the worst days. The results shown in Table 2 demonstrate the tremendous toll of NPC symptoms on daily

**Table 2 – Negative impact of symptoms on best and worst days**

	1 Low impact (few limitations)	2	3	4	5 High impact (unable to complete basic daily activities)	Weighted average
Best days	16.9%	12.0%	16.9%	22.9%	41.3%	3.4
Worst days	4.8%	9.6%	14.5%	22.9%	48.2%	4.0

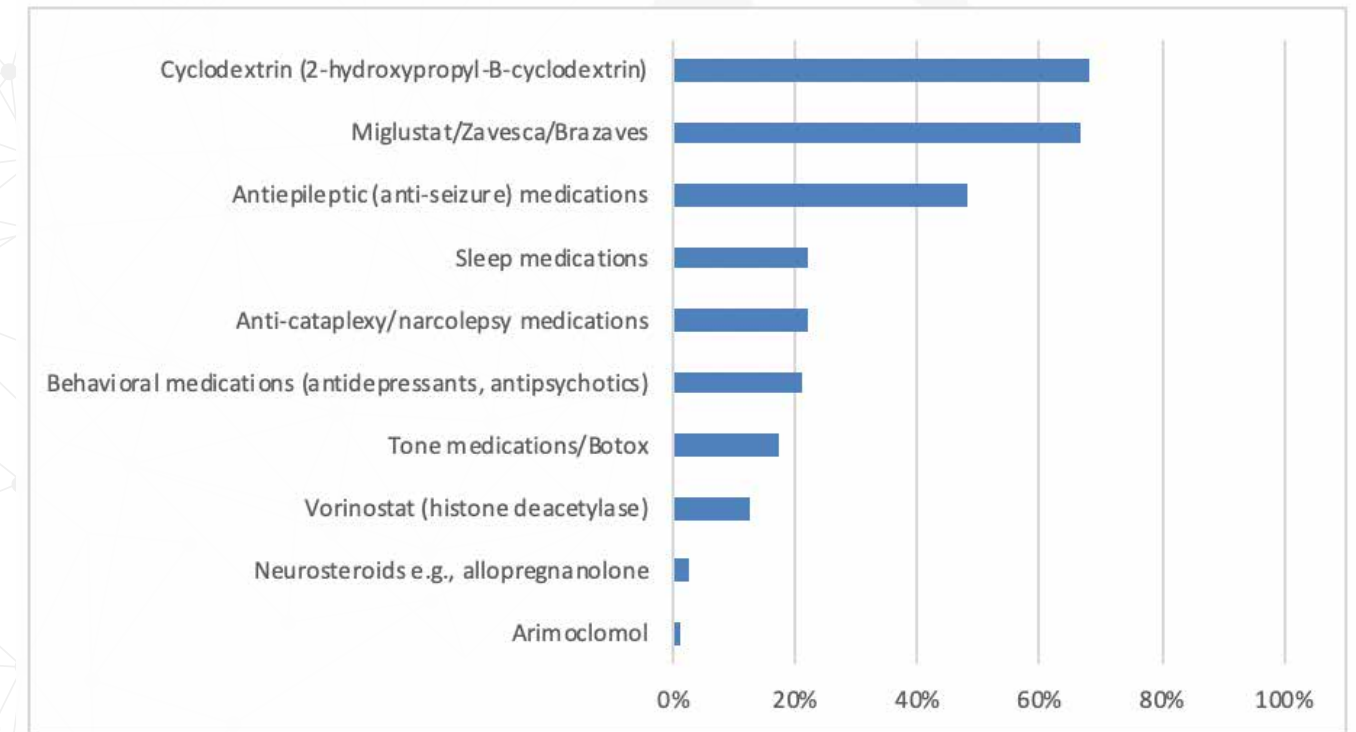
Many of the comments in the section above regarding which symptoms matter most refer to their impact on activities of daily living. Losing the ability to complete ADLs also has a substantial impact on caregivers.

The single mother of a girl diagnosed at age 9 said: *“I had to hire a live-in caregiver five days a week to assist me, to get her off and on the special needs school bus, to bathe her, dress her, to tube feed her, to give her routine medicines, et cetera... At around the age of 12 years old, when she was no longer able to talk, I would send a note to her teacher to explain what we did that weekend together. The lack of verbal communication was hard.”*

**TOPIC 2: Current approaches to treating Niemann-Pick Type C disease**



**Figure 2: Medications or experimental drugs currently or previously used by survey respondents**

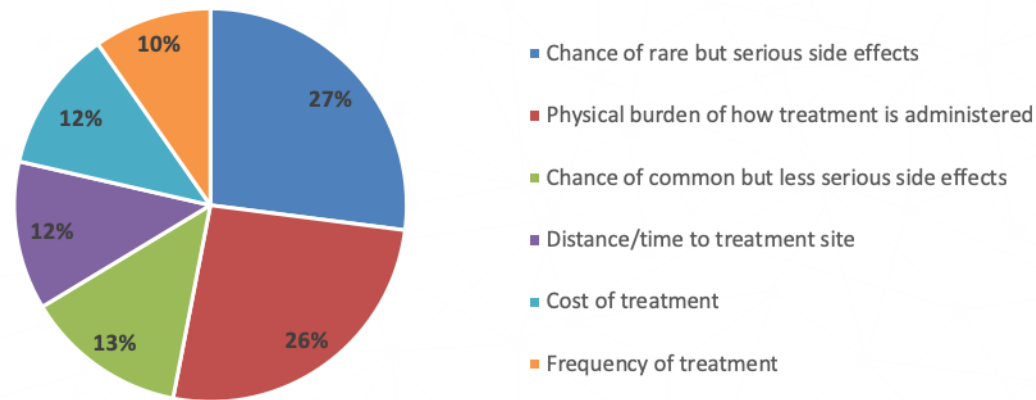


The survey asked what medications or experimental drugs patients had taken to treat symptoms of NPC. As shown in Figure 2 below, responses listed in order of frequency were: Cyclodextrins 67.9%, Miglustat 66.7%, antiepileptic/anti-seizure medications 48.2%, sleep medications 22.2%, behavioral medications (antidepressants or antipsychotics) 21%, tone medications or botox 17.3%, vorinostat (a histone deacetylase inhibitor) 12.4%, neurosteroids, e.g., allopregnanolone 2.5%, arimocloamol 1.2%. Cyclodextrins were not distinguished by individual name or mode of administration. The survey also asked what devices were used as a result of symptoms of NPC. Responses, listed in order of frequency, were: wheelchair 82.4%, gait supporter or walker 79.0%, Ankle foot orthosis brace 67.7%, gastrostomy tube 45.2%, pulmonary vest 41.9%, cough assist machine 40.3%, tablet or laptop to support speech communication 30.6%. Although the survey did not ask about the use of oxygen, several caregivers at the meeting noted that their child(ren) needed this as a part of their disease management.

Meeting participants were asked via a polling question to rank how much treatments improve the patient's quality of life on a four-point scale from 'not at all' to 'a lot'. More than half (56.7%) selected 'a lot', and an additional 36.7% selected 'a moderate amount.' Only 6.7% selected 'very little' and none selected 'not at all.'

Meeting participants were also asked via a polling question "When considering whether to receive a treatment for Niemann-Pick Type C disease, which three considerations would have the greatest influence on your decision?" The results from 57 participants are shown in Figure 3.

**Figure 3. Most important considerations when considering treatment**



Many meeting participants described a dizzying array of treatment approaches.

One mother of a boy diagnosed at 25 months of age said: "his bedroom was better equipped than most hospital rooms. We had a pulse ox, bipap, cough assist, oxygen concentrator, every conceivable wheelchair, play chair, stander, feeding pumps, adjustable bed, and he had every sensory toy, every specialist at his disposal. And he had everything except the freedom to move or to speak. During the course of his seven years, he had to have operations for hip dysplasia and more full leg cast. He was fed via a tube. Towards the end of his life, in the last few months, his med list contained 17 different medicines, compounds or therapies."

The mother of a 22-year-old with symptoms at age 5 but who was not diagnosed until age 15 said: "she was in occupational, speech and physical therapy. She also participated in aquatic and equestrian therapy and buddy baseball. Despite our best attempts to manage her symptoms and keep her active, she has continued to decline."

Comments from many meeting participants reinforced the perception that supportive (assist devices) and medical treatments improve patients' quality of life while also identifying drawbacks of available treatments. Medical treatments in particular were described as providing substantial benefits. Participants were asked not to identify the treatment by name. These comments are compiled below according to the type of treatment received.

### Medical treatments

The father of a 16-year-old who started treatment shortly after diagnosis at about age 9 said: "Given the stark neurological decline we observed in the previous year this treatment appears to have slowed the progression significantly from our perspective. However, while the neurological decline became less precipitous, it was perceptible nonetheless. His partial seizures increased in frequency, his balance continued to deteriorate, and signs of dysphagia and dysarthria came into place." Another treatment resulted in cognitive improvement in the form of greater awareness and alertness. Then he was enrolled in a double-blind clinical trial, and while they do not know whether he is receiving placebo or active treatment, the father said: "Within three to four months of the study, he swallowed solids with no difficulty and incidents of aspiration with liquids became less common. After 12 months into the trial, the dysphagia symptoms have virtually disappeared. His speech is clearer compared to last year, his gait is smoother compared to last year. Reports from teachers and his one-to-one aide at school show cognitive improvement as well, they all report that he's more focused, participates more in group activities and has improved short-term memory. The clinical trial we started in 2017 has given us hope, something we did not have at all, just two years ago."

The mother of a 26-year-old man with juvenile onset disease said: "When he would get sick more frequently and be in the hospital more frequently before treatment, he always would say to me, 'If I had my choice between life and death, I choose death,' because he wasn't living. He wasn't able to live and talk and communicate and do those things, and now since treatment, he's not once said that to me. He's happy and he's able to communicate, and he can talk to my parents. He has good days and bad days, and sometimes, he's quieter than others, but he ate his first McDonald's cheeseburger for the first time in four years. So you want to see him smile? Give him some food."

A 22-year-old woman with NPC said that during her five years of treatment "I've maintained my cognitive and physical abilities and some have even improved. I have a part-time job that I love... I socialize with my coworkers and sometimes go out on outings with them. I am able to drive myself to work as well as drive in my community..., I also work out three times a week doing cardio, lifting weights and working on my balance... My treatment has also let me regain the ability to do other physical tasks like walking in a straight line and using chopsticks... I am very independent. I take care of all my grooming and daily medications... My family and friends tell me I'm more talkative since my treatments began."

The mother of two children with NPC described her daughter's response to treatment this way: "Once we started several treatments ... she had multiple treatments ... she now is singing, she's laughing, she's dancing, she's walking, she's skipping, she's climbing ..."

A father said his son was diagnosed and treated at 5 months old. "He's almost completely asymptomatic still. He's 16 years old. On one hand I feel very fortunate that we happened to have been at a hospital where the geneticist knew about lysosomal storage diseases and was able to diagnose him."

The mother of a girl with symptoms beginning at 9 months of age said: *“Our first medical intervention was at 19 months. One month after diagnosis, we traveled from Los Angeles to Chicago every other week to receive a drug via compassionate use protocol to slow the neurological progression... At age three, we added an oral medication hoping to provide additional protection. In addition, [she gets] physical speech and occupational therapy twice a week, each. After beginning treatment, every aspect of her life improved incredible amounts. At 22 months, to our amazement, she began walking, her language exploded. She was no longer underweight. Her energy, comprehension, and interaction increased like someone flipped a light switch on. Two years later she continues making these gains in all areas... The benefits of her treatment far outweigh any downsides, yet there are challenges like difficulty controlling diarrhea from oral medications, missed activities for extra time to rest, and a demanding schedule that is packed with medical appointments and intervention services.”*

**Assistive devices for ambulation**

The mother of three children with NPC said: *“All three children eventually needed a walker... [they] needed a stroller for long distances and eventually a wheelchair was insisted upon by the school for their safety. To us this was like writing their death sentence because we knew that the less mobile they were, well if you don’t use it you lose it, so they would eventually not be able to walk well at all.”*

**Gastrostomy tube**

The mother of three children with NPC said: *“All three kids benefited from a feeding tube due to choking and they each had their trouble with that. Frequently leaking. Bed and clothing changes...”*

**Burden of managing disease**

The survey also asked what type of healthcare providers provide care and how much time is spent by the patient and caregiver actively managing the disease. Neurologists were the most common type of healthcare provider (seen by 92.8%), followed by pediatrician or internist (73.5%), physical therapist (65.1%), speech therapist (62.6%), gastroenterologist (44.6%), pulmonologist (39.8%), chiropractor (14.5%), homeopathic healthcare provider (8.4%), and acupuncturist (4.8%). Others, listed by 34.9% included primarily occupational therapists, as well as dieticians, social worker, geneticists, and many other medical specialists. Table 4 shows how much time patients and caregivers spend managing the disease; for example, appointments for medical care and physical or occupational therapy (including travel to and from), and delivery of home-based therapy. These results show a significant burden for both patients and caregivers and suggest that the burden falls heavily on caregivers.

**Table 4 – Hours per week spent actively managing disease**

Hours spent	% of patients	% of caregivers
0-5	30.5	21.8
5-10	28.0	24.4
10-15	18.3	12.8
More than 15	23.2	41

Comments from meeting participants provide further detail about the challenges and burden patients and caregivers face in obtaining necessary care:

A 22-year-old woman with adolescent onset NPC said: *“Currently, I fly to Chicago every two weeks for medical treatment. I have been doing this for almost five years.”*

The mother of a boy diagnosed at age 5 said: *“We travel two and a half hours one way every two weeks, missing a day of work and school, for him to receive treatment for his NPC... We have to travel to Iowa City for him to receive an IV of an immunosuppressive drug [for Crohn’s disease]. The infusion takes about three hours total for him to receive and it is an additional three hours total of driving, once again causing us to miss work and school.”*

The father of a 19-year-old diagnosed at age 6 said: *“We started on a trial at NIH six years ago, traveling 400 miles once a month. Fortunately, he was able to transfer to a closer hospital for those treatments three years ago. He has now had 107 lumbar punctures and the side effects include increased seizures, tiredness, incontinence and extreme back pain. Our lives are driven by NPC. Twice a week, we go to physical and occupational therapy. He also has speech once a week. The LPs every other week cause him to miss school and a weekend full of recovery. It’s hard to go anywhere... He will never eat a candy bar, drive a car, go on a date, hold a job or buy a house because of this horrible disease.”*

One mother said: *“Seven years after diagnosis, I have put my career as a registered nurse on hold to provide 24/7 care for [my daughter].”*



The mother of a 26-year-old enrolled in a trial said: *“We travel from Michigan to Chicago every two weeks. It takes two days of travel and treatment in which he misses out on daily life. He misses school, activities, time with his friends. Physical and occupational therapy every other week. Instead of being up and active, he is stuck in a car for 12 hours. The day after treatment is a full day of rest. Day one post-treatment, he can barely keep his eyes open, he’s quiet, he sleeps for most of the day and he cannot stay awake to eat safely. Fortunately, he had a G-tube placed in 2013 and we’ve been able to use that to keep up with his nutrition and hydration. By Sunday he perks up a little and by Monday he’s back to school. By the time he’s really doing well again, it’s time for another treatment.”*

One mother commented that because diagnosis was delayed until the disease was advanced, they decided not to get any treatment. *“We had to balance between the day programs that she loved to go to, and then missing that, the number of times we’d have to fly and go throughout everything else... you have to weigh the pros and cons and what it’s going to give back versus what you lose day-to-day, and it depends on where you are in that stage.”*

This comment illustrates both the need to balance benefits and risks and the importance of reversibility, determining at what point there is the potential to reverse loss and how that can be measured.

Indeed, another mother of a son who at age 19 had advanced disease enrolled in a trial despite being unsure if it would help. Within six months, she said, *“I could actually see a huge difference with his fine motor skills... After a year of treatment, he was able to get off the couch on his own, stand up, and walk, and he [hadn’t been able to] do that for years.”*

While many people ranked cost as a less important consideration than side effects in determining whether or not to get treatment, cost remains an important barrier to treatment for many families. One mother with 15 year-old-twins with NPC said, *“We’re on combination treatment, and we’ve done 220 lumbar punctures, 500 intravenous treatments. We’re also on another drug that’s an experimental medication. I think one of the things is that a lot of families face is cost of care. One of the drugs we’re on to date has cost \$2.5 million just for one drug. Seizure drugs are running \$10,000 a month each for each twin. My twins require 24/7 care. We have 10 different nannies on different shifts to take care of them, and this is all out-of-pocket costs. So I know a lot of families in here have tremendous financial burdens to take care of their kids and leave their jobs and so forth.”*

## POTENTIAL BENEFITS OF FUTURE TREATMENTS





Survey respondents were asked which one benefit of a new treatment for NPC would be most meaningful for patients and caregivers. In contrast to the discordant views of caregivers and patients in other chronic diseases such as Alzheimer’s disease, patients with NPC and their caregivers largely agreed on what they view as the most meaningful benefits of treatment. Results shown in Table 5 indicate that for both patients and caregivers, relief of neurological symptoms would be more meaningful than relief of physical symptoms and slightly more meaningful than a longer life span. Survey respondents and meeting participants also commented that these considerations may be weighted differently depending on the stage of disease.

**Table 5. Most meaningful benefit of a new treatment**

	Most meaningful to patients	Most meaningful to caregivers
Fewer neurological symptoms with the same life span	30.5%	34.6%
Longer life span with the same symptoms	25.6%	30.8%
Fewer physical symptoms with the same life span	12.2%	9.0%
Other*	31.7%	25.6%

\*Other desired benefits include improved quality of life and longer life with fewer neurological and other symptoms.

Meeting participants also noted that these considerations may be weighted differently depending on the patient’s stage of disease.

One father of a 16 year old with juvenile onset said: *“If somebody could tell me, ‘...He won’t ever be able to walk but he’ll be able to speak to you clearly and understand you...’ that would be much more important to me than walking.”*

The mother of a girl who began showing symptoms at 9 months old said: *“We were in a panic to do something to help her, realizing every passing day this disease is doing damage that cannot be undone. We wanted meaningful neurological intervention as quickly as possible. We were willing to go absolutely anywhere. With early symptoms at only 18 months, even a few months’ wait could allow NPC to ravage her system, debilitate her abilities, or worse.”*

The mother of a 26-year-old son with NPC who has been receiving treatments for 8 years added: *“I hope for less invasive approaches to treat NPC. I hope for a shorter treatment process that requires less travel and shorter recuperation times. I hope researchers are able to find a way to reverse more of the symptoms and to ultimately halt the progression of the disease.”*

Meeting participants were also asked via a polling question, “When thinking about the effects of a potential treatment, what ONE activity of daily living would the patient find most important to preserve or restore?” Results are shown in Table 6.

**Table 6. Most important activities to preserve or restore with treatment**

Activity	% of poll respondents selecting this as the most important activity to preserve or restore	
	Early infantile NPC (n=62)	Adult NPC (n=51)
Eating/drinking	38.7	39.2
Social activities	29.0	31.4
Personal care	9.7	19.6
Exercise/physical activities	16.1	3.9
School or work performance	6.4	5.9

The importance of eating and drinking reflects frequently cited concerns about swallowing as well as quality of life.

Said one mother: *“What is most meaningful to us right now with her is swallowing. We live in fear of pneumonia... of choking from not only eating the food but just choking on saliva at night when she’s sleeping.”*

A mother of a son born with an enlarged liver and spleen, diagnosed at age 7, and died at age 20 chose eating and drinking as the most important. She said: *“We were told that his body was storing cholesterol and so we put him on a cholesterol lowering regimen. We took his fried foods away from him... There were two decisions for him that if I could fix, I would go back and let that child eat all the French fries he could because he could only do it for another couple of years before he began choking rather terribly.”*

Preserving or restoring social activities is important for children, adolescents and adults with NPC. It intersects with eating and drinking for some families but also reflects the importance of finding treatments that improve cognition and language.

Said one mother: *“we feel those are the areas that would allow her to form meaningful relationships with other people and friendships, and we believe even though she could have mobility issues forever, if she could hold onto her language and her cognition, she would have the most fulfillment from her life.”*

The mother of two young men with adult onset NPC said: *“certainly both of my sons have become more socially isolated as this has progressed... they’ve slowly lost their social network. Their friends are moving on, they’re getting married, they’re having children, they’re buying houses, and my sons do not have any significant social activities at this point because they’re not dramatically brain injured, where there are lots of programs available, they’re not developmentally delayed, so they don’t fall into any category at this point, so there’s really nothing available for them. So I think the social activities category issue is huge.”*

### ***Translating findings about what matters most into the selection of endpoints***

The discussion around what meeting participants would find most meaningful in a future treatment points to specific clinically meaningful aspects of the disease that ideally would be captured with outcome measures used in clinical trials. For example, patients and caregivers expressed interest in endpoints that measure how much neurological decline has slowed or how much neurological function has been regained. Parents described children who went from being quiet and withdrawn to being much more communicative and engaged. Several parents also noted the importance of improving swallowing and avoiding silent aspiration. Other improvements associated with treatment included fewer seizures, less cataplexy, improved gait and walking abilities, improved speech, improved hearing, less tremor, less drooling, less ataxia resulting in fewer falls, and improved ability to eat.

A father of a child with NPC said *“The seizures are such an insidious part of the disease and once you start treating the seizures you get complications of the seizure meds. If you can affect the disease prior to seizures, I think that would be an enormous benefit.”*

Meeting participants acknowledged the difficulty of quantifying some of the most meaningful aspects of disease progression. For example, several parents spoke of their children “getting a light back in their eyes” or gaining the confidence to attempt difficult tasks. Parents also noted the need for different ways to quantitate certain abilities such as walking.

The mother of a seven-year-old girl diagnosed at 4 months of age said that during a recent evaluation of her walking abilities, the evaluator wrote that she could not walk a straight line forward. What the evaluator did not capture, according to the mother, was that *“she turned sideways on the line and took steps sideways... In that you can look and see that she has problem-solving skills that she didn’t have before. Her memory had improved because she was able to pay attention to the task. She was able to stay focused on what she was supposed to be doing.”*

### ***The need for multiple therapeutic options***

A common theme that emerged from meeting participants was the need for multiple therapeutic options to address the varied symptoms of the disease both between individuals and throughout disease progression.

One father of two children with NPC said it was nearly impossible to pick the most meaningful benefit from a choice of three (see Table 5): *“What I want is three drugs that do each one of those, and I want to be able to get those through the process and into my children and approved as fast as possible. So which one do I want? I want all of them, and that’s the whole point of the cocktail approach, is that I can’t pick just one of those.”*

The mother of a 3-year-old who is doing well with early intervention said: *“We hope for timely access to multiple therapies to form a cocktail approach to treatment. Our primary focus is stopping the disease in the brain, but we aspire to add in therapies to protect her liver, her spleen, and her lungs. We’ve accepted there will likely not be one magic answer to this complex condition and we are willing to take on multiple therapies to hit the multiple areas necessary.”*

The father of a 19-year-old with NPC added: *“we believe that a combination of disease-slowing compounds could give us time until cure is found.”*

### ***Accelerated access and compassionate use programs***

The survey asked whether people with NPC had ever received a treatment through an expanded access or compassionate use program. Nearly half (49.4%) answered ‘yes’, 45.8% answered ‘no,’ and 4.8% were not sure. However, access to these programs is limited and they are often associated with substantial burden for patients and family members.

For example, the mother of a boy diagnosed at 25 months of age said, *“Within four months we were fortunate enough to get him on compassionate IV use of a compound and it was at that time he finally began to add language, walked assisted, laughed, and for the first time he made some decisions for himself.”* A clinical hold on his compassionate use approval led to an eight-month period where he did not receive the drug. The mother continued, *“When you have such aggressive mutations, it meant his disease was very quickly able to take hold and we almost lost him. He could barely sit unassisted when he left the hospital in late 2012 at the age of three, within a week of restarting his infusion. He’s a true testament to what early treatment can do to delay the disease.”*

Another mother added, *“It took us three years to get his diagnosis at age eight. And we’re lucky enough that we got onto compassionate use... but what I hear over and over and over again from people trying to get on compassionate use is they can’t find a hospital willing to treat them. It infuriates me, because I went through that. I had to do five newscasts, go on the news five times. Beg, beg, beg somebody to help my son.”*



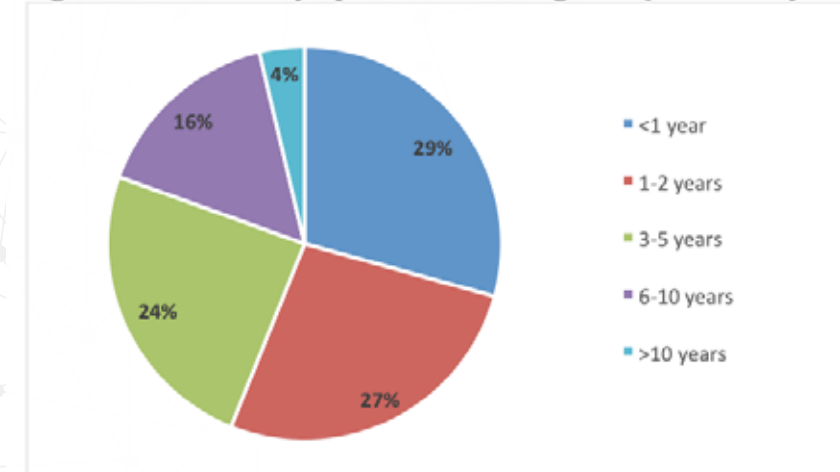
## DIAGNOSTIC CHALLENGES



A common theme throughout the meeting was the need for improved identification and diagnosis of NPC across the life span, from infancy through early adulthood. The heterogeneous presentation of NPC, non-disease specific symptoms, and individual disease progression make the possibility of identifying NPC early on highly unlikely – except in the rare cases of siblings where the younger, often pre-symptomatic child is diagnosed following an older, symptomatic sibling’s diagnosis.

According to survey results, diagnostic delay was common: 29.3% received a diagnosis within one year of symptom onset, 26.8% between and two years of symptom onset, 24.4% between three and five years of symptom onset, 15.8% between six and ten years of symptom onset, and 3.7% more than 10 years after symptom onset. Most (72.3%) had no relatives who had been diagnosed with the disease. Nearly half (49.4%) said they initially received an incorrect diagnosis before NPC was diagnosed. Incorrect diagnoses included Lyme disease, mononucleosis, neonatal hepatitis, meningitis, attention deficit disorder, bipolar disease, schizophrenia or schizo-affective disorder, autism spectrum disorder, Friedreich’s ataxia, muscular dystrophy, and others.

**Figure 4: Time from symptom onset to diagnosis (from survey responses)**



The survey also asked what symptoms first led parents or physicians to consider a diagnosis of NPC, as diagnoses are most commonly made by identifying a connection between multiple symptoms, rather than genetic testing. Respondents could select as many as applied. Enlarged spleen (53.0%) was the symptom most frequently selected as suggestive of NPC, followed by neurological symptoms (43.4%), other (43.4%), enlarged liver (30.1%), jaundice at birth (18.1%), speech delays/difficulty speaking (14.5%), loss of muscle control/movements (14.5%), hypotonia/low muscle tone at birth (13.2%). Common other responses were a sibling’s diagnosis, which several meeting participants noted led them to pursue whole exome testing for other children. Vertical gaze palsy was also a common response.

Comments of meeting participants reinforced and elaborated on these findings.

The mother of a five-year-old boy with NPC said that at age 2, her son developed perianal skin tags and was subsequently diagnosed with Crohn's disease. A gastrointestinal specialist noticed that he had an enlarged spleen and ordered a genetic workup, which led to the diagnosis of NPC. Said the mother: *"His case shows how important it is for every child with an enlarged spleen and Crohn's disease to be tested even in the absence of neurological symptoms."*

The mother of a girl who was born with jaundice and an enlarged liver, but who developed normally until second grade and was diagnosed at age 9 said: *"Symptoms of the disease began for her at second grade. Her handwriting started to become illegible. Her running seemed awkward, and she would fall down when laughing. Her speech started to slow down. She was asked by some of the kids, 'Why did she talk so funny?'"*

The father of two children with NPC disease said of his daughter: *"As an infant her doctor felt just the tip of her spleen, but it would come and go. Still that led to specialists and many tests. Including a painful bone marrow scrape to check her for leukemia. They found no cause, decided it was likely a viral reaction and we were told to go home and enjoy our daughter. But then at the age of five we were stunned to hear that she was falling well behind the other children at school. And that started a three-year journey of seeing specialist after specialist with no answers until that terrible day we learned that she had NPC and were told that there were no treatments available and we had only another five or six years with her."*

The mother of a girl with adult-onset NPC described how her daughter was diagnosed with bipolar disorder, became psychotic and then was diagnosed with schizoaffective disorder. Eleven years later, her doctor went to a convention where he learned about genetic illnesses that mimic bipolar and realized that NPC could be the reason for her psychiatric symptoms.

The mother of a boy diagnosed at 25 months of age said: *"He was born with a catch-all diagnosis of cholestatic liver disease and an enlarged spleen. He suffered bloodwork every few days for the first six weeks of his life... we couldn't rule out biliary atresia, so he had to fly to Cincinnati at 10 weeks old to consider doing a procedure [to test for that]. They ran a full genetic panel on him at that time, but nobody tested for NPC. So, he was labeled failure to thrive. Specialized formula was needed. He had low muscle tone and his eyes even seemed off. And later we learned what I was describing was supranuclear gaze palsy and we moved for what would have been the second of four states in three years to seek answers and treatment. A pediatrician in Vermont stepped in and she got him tested for NPC and at the same time hooked us up with every conceivable support service."*

The mother of a 22-year-old with NPC said: *"From the age of five to 15, she went to 14 doctors in four states to get a diagnosis for Niemann-Pick Type C."*

Many meeting participants described good outcomes for individuals diagnosed and treated early. They advocated for raising awareness among health care providers about signs and symptoms that may suggest NPC as well as increased genetic screening of newborns, both with the aim of supporting early diagnosis, a point on which there is consensus among many NPC experts.

Some meeting participants described good outcomes for individuals diagnosed and treated before signs or symptoms of the disease were apparent. There was a general agreement among meeting attendees regarding the need for increased awareness among health care providers about early signs and symptoms that may suggest NPC as well as the need for newborn screening, both with the aim of supporting early diagnosis and intervention, a point on which there is consensus among many NPC experts. **(8)** Some meeting participants spoke about a multi-stakeholder coalition established in June 2017 with the goal of adding NPC to the Recommended Uniform Screening Panel (RUSP), a list of disorders that the federal government recommends states include in their newborn screening programs. A proven assay using dried blood samples is currently available **(9)** and the NPC Newborn Screening Coalition **(10)** is awaiting the launch of a pilot study of newborn screening for NPC in the fall of 2019 in New York State.

One mother added, *"I think as genetic testing gets better, as our diagnoses maybe gets better, we're gonna find that there are more and more adults out there who have this disease and have been living with it, managing symptoms that are not quite as severe but certainly dealing with it. And I think that maybe beginning to include more psychiatric kinds of things would be appropriate as well."*

Another mother of a 19-year-old young man with NPC described how although as an infant he presented with delayed but prolonged jaundice, he didn't develop neurological symptoms until age 14 or 15. She suggested that delayed or prolonged jaundice might be an early indicator of disease, and suggested efforts to think through other early indicators that could accelerate identification of affected individuals.

Another mother commented that since her daughter's enlarged spleen suggested a possible lysosomal storage disorder, the lysosomal storage panel the doctors ran did not include NPC and came back negative. *"We eventually got our diagnosis through whole exome sequencing, but we couldn't get to that point until she had probably been tested for ... She probably had had about 30 lab draws already in her life and had been tested for probably about 100 different things already."* The mother advocated including NPC on more screening panels.

Many other participants agreed on the need for screening. One mother said: *"in order to give all of these patients the best quality of life, we need to find the disease before there's any signs or symptoms of the disease. And I think when we are able to do that, we will be able to render the disease chronic. And I think the best way to do that in our public health system the way it is today is through newborn screening."*



## WILLINGNESS TO PARTICIPATE IN RESEARCH



Patients and families with NPC are desperate for breakthroughs and many are willing to participate in research. This was evident from the survey data, which show that a high percentage (42.3%) of respondents have participated in a clinical trial. This percentage is especially high given that 23.0% of survey respondents filled out the survey on behalf of people who had passed away from NPC, some of whom passed away ten or more years ago before trials became available. Many respondents indicated that they have participated in more than one type of trial: 88.6% have been in intervention trials and 57.1% in observational trials.

Those who answered that they had participate in a trial were asked to indicate their primary reason for participation. More than half (51.4%) cited a lack of treatment options; 14.3% cited a desire to help others with NPC, and 2.9% said it was suggested by a doctor. Another 14.3% cited other reasons, including the desire to find new and less invasive treatments and cures.

Of the 27 survey respondents who have not participated in a trial before and answered the question “*Would you consider joining a clinical trial?*” a large majority (77.8%) said ‘yes.’ This data point and the already high level of trial participation among the NPC community emphasize patients’ and families’ commitment to research to drive the development of treatments.

The survey also asked which factors were important in their decision to participate in a clinical trial and if those factors would affect them a little, a moderate amount, or a lot. Table 7 shows the results for this question, presented as weighted averages in order of their importance based on how much the factor would matter. The following scale was used for this question:

- 1 = Factor would matter a little
- 2 = Factor would matter a moderate amount
- 3 = Factor would matter a lot

**Table 7: Factors important in the decision to participate in a clinical trial**

Factor	Weighted average
Whether the treatment could improve my quality of life	2.81
Possibility of receiving the new treatment vs. a placebo or current treatment	2.48
Whether there might be negative side effects of the treatment	2.26
How long it will take to get to the trial site and how many times you have to go	1.89
Whether the trial requirements (protocol) are difficult or easy to follow	1.85
How long the study lasts	1.52

Comments from meeting participants described some of the advantages patients and families realized as the result of participating in clinical trials.

The mother of a 22-year-old whose symptoms began at age 5 said: *“We have been participating in an experimental treatment over the last four years. After treatment, we see small improvements for three to four days, a small smile, a few words, an attempt to wipe her own nose, the ability to hold her head up a little better or just a little improvement in muscle control, is what makes this five hour drive worthwhile.”*

The father of two girls with NPC said: *“Shortly after diagnosis, we began treatment, flying from Austin, Texas to Chicago every two weeks. We did this for nine months before opening a trial site in our hometown. For my family, for my girls, our treatment has been a true blessing. [Our older daughter] has stabilized. Her therapists are impressed with her progress. While she may not be able to keep up with her peers, she is not regressing. [Our younger daughter] began treatment at 20 months old. At the time, she was the youngest child to receive treatment near asymptotically. By all accounts, she’s neurotypical. She speaks two languages, she dances, she does gymnastics... She is the poster child for early intervention and treatment.”*

The mother of a boy born with an enlarged liver and spleen and who was eventually diagnosed with NPC at 15 months of age when he lost the ability to stand and was referred for genetic testing said: *“We knew we couldn’t stand by and continue to watch our son lose all of his abilities. We began an experimental treatment in February 2018 and added PT, OT and speech to the list of his weekly therapies. He is almost three years old and his week consists of twice weekly sessions of PT, OT and speech.”*

The mother of a 13-year-old boy with NPC diagnosed at age 4 said that even though her son had few symptoms, at age 8 he started a phase 1 trial despite there being little information about the risks involved, *“We didn’t know if it was going to kill him, we didn’t know. But you know what? I would take a 3% [chance of better outcome], because I have 0% without it.”* She went on to say, *“He’s been on a treatment for five years now, this month, and I have to say that I truly, truly believe he is doing as well as he is doing because we have this treatment and because of all the hard work... There are sacrifices with it, you know, and we had to fly to Maryland every three weeks for two years with a little baby and everything and it’s worth every, every second.”*

## INCORPORATING PATIENT INPUT INTO A BENEFIT-RISK FRAMEWORK FOR NIEMANN-PICK TYPE C DISEASE



In 2013, the FDA published a draft implementation plan for a structured approach to benefit-risk assessment in drug regulatory decision making (11.), and updated this plan in 2018 (12.). The latter document responds to a requirement of the 21st Century Cures Act that the agency issue guidance on how patient experience data will be incorporated into the structured benefit-risk assessment framework to inform regulatory decision making. This framework calls for assessing four decision factors: Analysis of Condition, Current Treatment Options, Benefit, and Risk and Risk Management. When completed for a specific product, it summarizes each decision factor and explains the FDA's rationale for its regulatory decision. The benefit-risk framework is important for both regulatory and treatment decisions.

The PFDD process is designed to allow the patient voice to help construct a benefit-risk framework for use in the evaluation of new treatments. People living with the disease have a unique perspective on the dimensions that are most important and critical to regulatory decision making, the unmet medical needs of others with their condition, and the benefit-risk tradeoffs that may be acceptable across the continuum of the disease. Their input should be the foundation of therapeutic development, especially in terms of developing treatments that are clinically meaningful and that address aspects of disease that are most critical to people living with the disease. Moreover, by reflecting on the perspective of people with NPC, drug developers will be better able to design clinical trials with a high chance of success. It will be important to further define the benefit expectations and risk tolerance for varying treatment options to better characterize these tradeoff decisions faced by patients, families and healthcare providers, as well as regulators.

The input provided by people with NPC and their caregivers at the NPC PFDD Meeting and through the pre-meeting survey is summarized here in this sample framework (Table 8) to provide an understanding of the benefit/risk aspects for two of these decision factors: Analysis of Condition and Current Treatment Options. This sample framework is likely to evolve over time and could be incorporated into a benefit-risk assessment framework for a drug under review.

This externally-led NPC PFDD meeting demonstrates that people with NPC are highly engaged and enthusiastic about working with the FDA and drug developers to advance better treatments for this debilitating disease.

**Table 8: Sample benefit-risk dimensions for Niemann-Pick Type C disease**

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
<b>Analysis of Condition</b>	<p>Niemann-Pick Type C (NPC) disease is a rare, progressive, and fatal autosomal-recessive lysosomal storage disorder that is inherited in an autosomal recessive manner. Disease onset is highly variable, ranging from early fetal life through adulthood with a range of systemic and neurological symptoms. Manifestations, speed of progression, and severity of disease are also highly variable. Death is often associated with pneumonia, brought on by lung damage combined with swallowing difficulties leading to aspiration.</p> <p>Because of the rarity of NPC and the fact that most symptoms are non-specific and vary over time, diagnosis and intervention may be substantially delayed.</p>	<p>NPC is a progressive neurovisceral disorder that may cause serious physical and neuropsychiatric disability, resulting in a reduced quality and length of life and substantial burden to families. The severity, insidious nature, and unpredictability of NPC take a high physical and emotional toll of NPC on patients and families, producing a high unmet need for more therapeutic options.</p>
<b>Current Treatment Options</b>	<p>There is no cure for NPC. Current treatments are primarily symptomatic and may be associated with significant adverse effects. Disease-modifying treatments in development are being evaluated in clinical trials, and medications approved for other conditions are available to some patients through expanded access programs. These treatments have shown some signs of efficacy when started early in the disease course. However, access may be limited by geographical and cost barriers.</p>	<p>Drug treatments are urgently needed to slow disease progression and reverse the most debilitating symptoms of NPC. Improved screening and early diagnosis are also needed to facilitate entry into clinical trials and treatment programs. Clinical outcome measures that assess aspects of the disease that are meaningful to patients are also required to accelerate the development of new therapies.</p>

## CONCLUSION

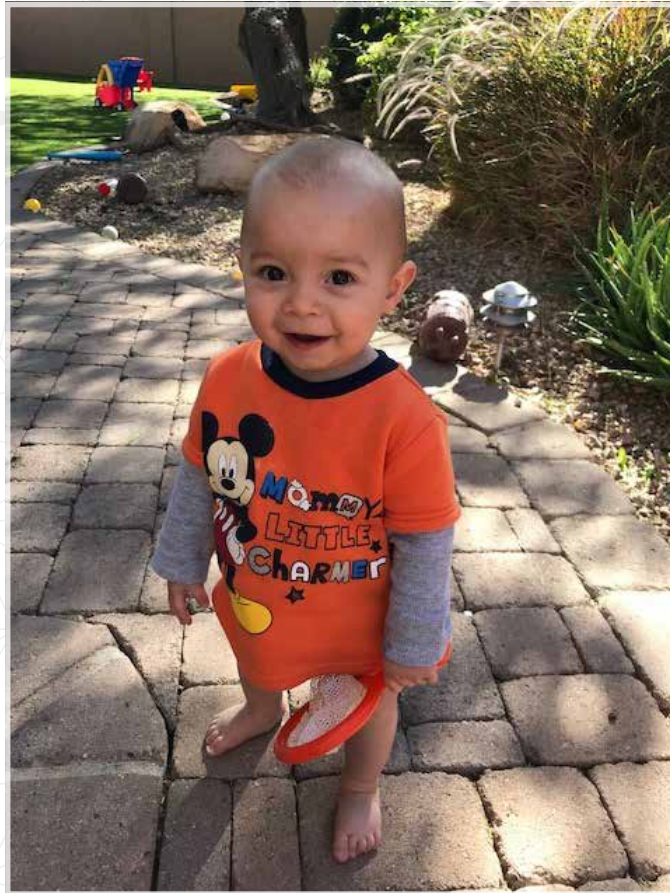


*Key take-aways from the NPC PFDD meeting can be summarized as follows:*

1. NPC is a horrible disease that has far-ranging effects on both patients and their families.
2. There is an urgent need for early diagnosis (including newborn screening), treatments, and early intervention.
3. Better characterization of progression and patterns of disease through natural history studies are needed to improve the design and conduct of clinical trials. It is important to note, however, that the availability of true natural history data is limited because the majority of NPC patients are currently on or have previously used one or more treatments or experimental therapies.
4. Patients with NPC and their families are eager to participate in expanded access and compassionate use programs as well as research studies and clinical trials.
5. New outcome assessment measures are needed that incorporate what patients and caregivers consider meaningful.
6. Collaboration among patient advocacy groups, researchers, regulators, and drug developers is the cornerstone to progress.
7. Treatment approaches that allow the use of multiple therapies to address different symptoms should be considered.
8. Importance of a framework for extrapolation of results across trials as well as master protocol considerations for multiple sponsors within an overarching study plan.
9. There is a need for refined benefit-risk assessment studies to aid decision making.



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## APPENDIX 1: Meeting Agenda

### Niemann-Pick Type C Disease Patient-Focused Drug Development Meeting

Monday, March 18, 2019  
 10:00 a.m. – 4:00 p.m.  
 College Park Marriott Hotel & Conference Center  
 Meeting Rooms 2110, 2111, and 2112  
 Hyattsville, MD

9:00 – 10:00 a.m.	Registration
10:00-10:10 a.m.	Welcome Remarks Sean Kassen, PhD Director, Ara Parseghian Medical Research Fund
10:10 – 10:20 a.m.	Meeting Agenda and Desired Outcomes Timothy R. Franson, MD, Moderator
10:20 – 10:35 a.m.	FDA's Approach to Rare Disease Drug Development and the Importance of the Patient Voice Dragos Roman, MD Associate Director, Division of Gastroenterology and Inborn Errors Products, Food and Drug Administration
10:35 – 10:55 a.m.	Overview of Niemann-Pick Type C Disease and Current Treatments Marc C. Patterson, MD Professor of Neurology, Pediatrics and Medical Genetics, Mayo Clinic Children's Center
10:55 – 11:00 a.m.	Panel Format Description & Demographics Poll Timothy R. Franson, MD, Moderator
11:00 a.m. – 11:30 a.m.	Panel on Discussion Topic 1: Symptoms of Niemann-Pick Type C disease (late infantile and juvenile forms) and daily impacts that matter most Panel of Niemann-Pick Type C patients and patient representatives

11:30 a.m. – 12:05 p.m.

Facilitated Discussion: Topic 1  
 Patients and patient representatives in the audience

12:05 p.m. – 1:00 p.m.

Lunch

1:00 – 1:05 p.m.

Afternoon Welcome  
 Timothy R. Franson, MD, Moderator

1:05 – 1:40 p.m.

Panel on Discussion Topic 2: Current approach to treating Niemann Pick Type C (late infantile and juvenile forms)  
 Panel of Niemann-Pick Type C patients and patient representatives

1:40 – 2:20 p.m.

Facilitated Discussion: Topic 2  
 Patients and patient representatives in the audience

2:20 – 2:50 p.m.

Panel on Discussion Topic 3: Symptoms of Niemann-Pick Type C disease (early infantile and adult forms) and daily impacts that matter most  
 Panel of Niemann-Pick Type C patients and patient representatives

2:50 – 3:30 p.m.

Facilitated Discussion: Topic 3  
 Patients and patient representatives in the audience

3:30 – 3:50 p.m.

Open Public Comment

3:50 – 3:55 p.m.

Key Points from Today's Discussion  
 Timothy R. Franson, MD, Moderator

3:55 – 4:00 p.m.

Closing Remarks  
 Sean Kassen, PhD  
 Director, Ara Parseghian Medical Research Fund

## APPENDIX 2: Meeting Speakers and Panel Participants

All speakers listed in the order in which they presented. Niemann-Pick Type C disease is abbreviated as “NPC”.

### Opening Speakers

- Sean Kassen, Ph.D., Director, Ara Parseghian Medical Research Fund
- Timothy R. Franson, M.D., Principal, Faegre Baker Daniels Consulting
- Dragos Roman, M.D., Associate Director, Division of Gastroenterology and Inborn Errors Products, U.S. Food and Drug Administration
- Marc C. Patterson, M.D., Professor of Neurology, Pediatrics, and Medical Genetics, Mayo Clinic Children’s Center

### Panel 1 Panelists

- Samantha Berns, person with NPC
- Jenna Weets, mother of Jeg, a child with NPC
- Phil Marella, father of Andrew and Dana, two children with NPC
- Liz Heinze, mother of Tyler, Katie, and Faith, three children with NPC
- Judy Desouza, mother of Bryanna, a child with NPC
- Cindy Parseghian, Mother of Michal, Marcia, and Christa, three children with NPC

### Panel 2 Panelists

- Sara McGlocklin, mother of Marian, a child with NPC
- Alex Kray, father of Jasper, a child with NPC
- Sean Recke, father of Adam, a child with NPC
- Mary Haynes, mother of Rebekah, a child with NPC
- Chris Andrews, father of Abby and Belle, two children with NPC
- Amy Whaley, mother of John Michael, a child with NPC

### Panel 3 Panelists

- Debbie Kaflowitz, mother of Rachael, a child with NPC
- Michelle Miller, mother of Parker, a child with NPC
- KayLa Miller, mother of Kamryn, a child with NPC
- Shannon Reedy, mother of Chase, a child with NPC
- DeAnna Odeh, mother of Osama, a child with NPC
- Gail Koujaian, mother of Alec and Hayley, two children with NPC
- Alec Koujaian, a person with NPC

### Panel Alternates

- Melissa King, mother of Lee, a child with NPC
- Rebecca Spencer White, mother of Jonathan, a child with NPC
- Meghann Ferguson, mother of Liam, a child with NPC

## APPENDIX 3: Meeting Polling Questions

### Test Question

1. What is your favorite color?
  - a. Red
  - b. Orange
  - c. Yellow
  - d. Green
  - e. Blue
  - f. Purple

### Demographic Questions

1. Which best describes you?
  - a. Person with Niemann-Pick Type C
  - b. Parent or caregiver of person with Niemann-Pick Type C
2. What type of Niemann-Pick Type C do you (or your child) have?
  - a. Visceral-neurodegenerative / early infantile form (typical onset at <2 years old)
  - b. Neurodegenerative / late infantile form (typical onset between 2 and 6 years old)
  - c. Neurodegenerative / juvenile form (typical onset between 6 and 15 years old)
  - d. Psychiatric-neurodegenerative / adult form (typical onset at >15 years)
  - e. Not sure

### Topic 1 Questions

1. Which one symptom of Niemann-Pick Type C has the greatest impact on your (the patient’s) daily life?
  - a. Ambulation / walking difficulties
  - b. Cognitive (thinking and learning) impairment
  - c. Difficulty swallowing
  - d. Hearing problems
  - e. Impacts on fine motor skills
  - f. Liver disease / failure
  - g. Respiratory disease / breathing problems
  - h. Seizures
  - i. Speech problems
  - j. Vertical gaze palsy / eye movement issues

2. What symptom(s) first led you or your physicians to consider a diagnosis of Niemann-Pick Type C disease? Select up to three.

- a. Enlarged liver
- b. Enlarged spleen
- c. Jaundice at birth
- d. Hypotonia / low muscle tone at birth
- e. Loss of control of muscle / movements
- f. Neurological symptoms
- g. Pulmonary / lung disease
- h. Speech delays / difficulty speaking

### Topic 2 Questions

1. On a scale of 1-4, how much do your treatments improve your (the patient's) quality of life?

- a. Not at all
- b. Very little
- c. A moderate amount
- d. A lot

2. When considering a potential new treatment for Niemann-Pick Type C disease, which one benefit would you consider to be most meaningful?

- a. Longer life span with same symptoms
- b. Fewer physical symptoms with same life span
- c. Fewer neurological symptoms with same life span

3. When considering whether to receive a treatment for Niemann-Pick Type C disease, which considerations would have the greatest influence on your decision? Choose up to three.

- a. Chance of rare, but serious side effects
- b. Chance of common, but less serious side effects
- c. Cost of treatment
- d. Frequency of treatment
- e. Distance / time to treatment site
- f. Physical burden of how treatment is administered

### Topic 3 Questions

1. [For those representing patients with early infantile NPC] Which one symptom of Niemann-Pick Type C has the greatest impact on your (the patient's) daily life?

- a. Ambulation / walking difficulties
- b. Cognitive (thinking and learning) impairment
- c. Difficulty swallowing
- d. Hearing problems
- e. Impacts on fine motor skills
- f. Liver disease / failure
- g. Respiratory disease / breathing problems
- h. Seizures
- i. Speech problems
- j. Vertical gaze palsy / eye movement issues

2. [For those with adult NPC or representing patients with adult NPC] Which one symptom of Niemann-Pick Type C has the greatest impact on your (the patient's) daily life?

- a. Ambulation / walking difficulties
- b. Cognitive (thinking and learning) impairment
- c. Difficulty swallowing
- d. Hearing problems
- e. Impacts on fine motor skills
- f. Liver disease / failure
- g. Respiratory disease / breathing problems
- h. Seizures
- i. Speech problems

3. [For those representing patients with early infantile NPC] What symptom(s) first led you or your physicians to consider a diagnosis of Niemann-Pick Type C disease? Select up to three.

- a. Enlarged liver
- b. Enlarged spleen
- c. Jaundice at birth
- d. Hypotonia / low muscle tone at birth
- e. Loss of control of muscle / movements
- f. Neurological symptoms
- g. Pulmonary / lung disease
- h. Speech delays / difficulty speaking

4. [For those with adult NPC or representing patients with adult NPC] What symptom(s) first led you or your physicians to consider a diagnosis of Niemann-Pick Type C disease? Select up to three.
- Enlarged liver
  - Enlarged spleen
  - Jaundice at birth
  - Hypotonia / low muscle tone at birth
  - Loss of control of muscle / movements
  - Neurological symptoms
  - Pulmonary / lung disease
  - Speech delays / difficulty speaking
5. [For those representing patients with early infantile NPC] When thinking about the effects of a potential treatment, what activity of daily living would you (the patient) find most important to preserve or restore?
- Eating/drinking
  - Exercise or participation in sports/physical activities
  - Personal care such as dressing, bathing, using the toilet
  - School or work performance
  - Social activities
6. [For those with adult NPC or representing patients with adult NPC] When thinking about the effects of a potential treatment, what activity of daily living would you (the patient) find most important to preserve or restore?
- Eating/drinking
  - Exercise or participation in sports/physical activities
  - Personal care such as dressing, bathing, using the toilet
  - School or work performance
  - Social activities

### Niemann-Pick Type C Patient-Focused Drug Development Meeting Pre-Meeting Survey

Welcome to the Niemann-Pick Type C disease patient-focused drug development (PFDD) survey. The purpose of this survey is to collect information on people's experiences living with Niemann-Pick Type C disease including their symptoms, treatments, and the impact of the disease on daily life. This is your opportunity to make sure your voice is heard so that the U.S. Food and Drug Administration understands what it is like to live with Niemann-Pick Type C disease.

This initiative is being organized by the Ara Parseghian Medical Research Fund. The data from this survey will be used to plan the Niemann-Pick Type C PFDD meeting on Monday, March 18, 2019 and for a report to be published after the meeting. Your responses—without your personally identifiable information—may be used for these purposes and/or shared with the Ara Parseghian Medical Research Fund's partners in the PFDD initiative.

Your participation in this survey is optional and if you start the survey, you can stop at any time. If you have questions or concerns about the survey, please contact the Ara Parseghian Medical Research Fund at [skassen@nd.edu](mailto:skassen@nd.edu).

To view the full informed consent, child assent, and parental permission forms, please click the links below.

- [General informed consent form](#)
  - [Assent for child participation](#)
  - [Parental permission for child participation](#)
1. By selecting "I consent" below, you voluntarily agree to participate in this study. If you are completing this survey on behalf of a child or impaired adult with Niemann-Pick Type C disease, clicking "I consent" will constitute parental permission for the child's data to be used in this research.
    - [I consent](#)
    - [I do not consent](#)

[Only those who click "I consent" will be able to continue the survey]

## PART I: CONTACT AND BACKGROUND INFORMATION

Parents or representatives completing this survey on behalf of a child with Niemann-Pick Type C disease should provide their contact information, not the child's.

2. Your name

First name: \_\_\_\_\_

Last name: \_\_\_\_\_

3. Your phone number and/or email address

Phone Number \_\_\_\_\_

Email Address \_\_\_\_\_

4. Do you live in the United States?

- Yes
- No

5. (If they answer "Yes" to question 1.3) Please enter your ZIP/postal code: \_\_\_\_\_

6. Please select the option that best describes you.

- Person with Niemann-Pick Type C disease
- Parent, guardian, or caregiver of a person with Niemann-Pick Type C disease

7. Are you a current caregiver of a person with Niemann-Pick Type C disease or a former caregiver of a person who passed away from the disease? Note: all caregivers should complete the survey.

- Current caregiver
- Former caregiver

8. If you are interested in attending the March 18, 2018 Niemann-Pick Type C disease Patient-Focused Drug Development meeting in Hyattsville, Maryland, would you be willing to be a panelist? Note: only U.S. residents are eligible to be panelists.

- Yes, I'm willing to serve as a panelist and agree to let the Ara Parseghian Medical Research Fund contact me about this opportunity
- I'm interested in attending the meeting, but don't want a speaking role
- I'm just filling out the survey, not interested in attending the meeting

9. How did you learn about this survey?

- Niemann-Pick foundation or advocacy organization website
- Doctor or other healthcare provider
- Friend or family member
- Niemann-Pick Type C PFDD Meeting website
- Other Internet site or social media
- Flyer or other printed material
- Other (please describe)

10. Would you like to receive future information about the PFDD initiative and other research opportunities from the Ara Parseghian Medical Research Fund and its partners?

- Yes
- No

## REMINDER

The primary purpose of this survey is to collect information on viewpoints of people with Niemann-Pick Type C disease (NPC). If you are a parent, guardian, or caregiver of a person with NPC, please answer these questions on their behalf. If you have more than one child with NPC, please fill out a separate survey for each child.

There are a few questions that ask about the caregiver viewpoint which are clearly marked as such. All other questions should be answered on behalf of the person with Niemann-Pick Type C disease.

## PART II: DEMOGRAPHIC INFORMATION

11. Sex of person with Niemann-Pick Type C disease

- Male
- Female
- Other

12. Ethnicity of person with Niemann-Pick Type C disease

- Hispanic/Latino
- Not Hispanic/Latino

13. Race of person with Niemann-Pick Type C disease (select as many as apply)

- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or Other Pacific Islander
- White
- Other

14. Age of person with Niemann-Pick Type C disease. Note: if you are a former caregiver, please select the age of the person when they passed away.

- Less than 2 years
- 2-5 years
- 6-12 years
- 13-18 years
- 19-29 years
- 30-39 years
- 40-49 years
- 50-59 years
- 60 years or older

### PART III: DISEASE BACKGROUND

15. Age when symptoms of Niemann-Pick Type C disease first began

- Less than 2 years
- 2-5 years
- 6-12 years
- 13-18 years
- 19-29 years
- 30 years or older

16. Age when neurological symptoms of Niemann-Pick Type C disease first began. Examples of such symptoms include developmental delays, ataxia, and vertical gaze palsy, among others.

- Less than 2 years
- 2-5 years
- 6-15 years
- 16-29 years
- 30 years or older

17. How long ago were you diagnosed with Niemann-Pick Type C disease?

- Less than 1 year
- 1-5 years
- 6-10 years
- More than 10 years

18. How much time passed between when your Niemann-Pick Type C disease symptoms started and when you were officially diagnosed?

- Less than 6 months
- 6-12 months
- 1-2 years
- 3-5 years
- 6-10 years
- More than 10 years

19. Do you have any relatives who have/had Niemann-Pick Type C disease?

- Yes
- No

20. (If they answered “Yes” to the above question). Please select the option that best describes that relative’s/those relatives’ relation to you. For those with multiple family members who have/had Niemann-Pick Type C disease, please select as many as apply.

- Brother or sister
- Cousin
- Parent
- Aunt or uncle
- Other (please specify)

### PART IV: DISEASE SYMPTOMS AND IMPACT ON DAILY LIFE

21. What type of Niemann-Pick Type C disease do you have?

- Visceral-neurodegenerative / early infantile form (typical onset at <2 years old)
- Neurodegenerative / late infantile form (typical onset between 2 and 6 years old)
- Neurodegenerative / juvenile form (typical onset between 6 and 15 years old)
- Psychiatric-neurodegenerative / adult form (typical onset at >15 years)
- Not sure

22. Of all of the Niemann-Pick Type C disease symptoms that you experience, which do you consider to have the most significant impact on your (the patient’s) daily life? Please choose up to three symptoms that have the most impact and rank them 1-3.

- Ambulation / walking difficulties
- Cognitive (thinking and learning) impairment
- Difficulty swallowing
- Hearing problems
- Impacts on fine motor skills
- Liver disease / failure
- Respiratory disease / breathing problems
- Seizures
- Speech problems
- Vertical gaze palsy / eye movement issues

23. Caregiver perspective only (please skip if you are a person with Niemann-Pick Type C disease). Of all of the Niemann-Pick Type C disease symptoms that your child experiences, which do you consider to have the most significant impact on your (the caregiver’s) daily life? Please choose up to three symptoms that have the most impact and rank them 1-3.

- Ambulation / walking difficulties
- Cognitive (thinking and learning) impairment
- Difficulty swallowing
- Hearing problems
- Impacts on fine motor skills
- Liver disease / failure
- Respiratory disease / breathing problems
- Seizures
- Speech problems
- Vertical gaze palsy / eye movement issues

24. What symptom(s) first led you or your physicians to consider a diagnosis of Niemann-Pick Type C disease? Select as many as apply.

- Enlarged liver
- Enlarged spleen
- Jaundice at birth
- Hypotonia / low muscle tone at birth
- Loss of control of muscles / movements
- Neurological symptoms

- Pulmonary/lung disease
- Speech delays / difficulty speaking
- Other (please specify)

25. Did you initially receive an incorrect diagnosis before Niemann-Pick Type C disease was diagnosed?

- Yes
- No

26. (If respondents answer “Yes” to question 25) What incorrect diagnosis/diagnoses did you receive?

[FREE TEXT RESPONSE]

27. What activities of daily living are most impacted by your Niemann-Pick symptoms?

- Eating/drinking
- Exercise or participation in sports/physical activities
- Household chores or activities
- Personal care such as dressing, bathing, using the toilet
- School or work performance
- Social activities
- Travel
- Other (please specify)

28. On a scale of 1-5, how much do your disease symptoms negatively impact your life on the best days?

A score of 1 is minimal impact (a few limitations on daily activities) and a score of 5 is high impact (completely unable to complete basic daily activities).

\_\_\_\_\_ Level of impact

29. On a scale of 1-5, how much do your disease symptoms negatively impact your life on the worst days? A score of 1 is minimal impact (a few limitations on daily activities) and a score of 5 is high impact (completely unable to complete basic daily activities).

\_\_\_\_\_ Level of impact

## PART V: TREATMENTS

30. Have you ever taken any of the following medications or experimental drugs to treat the symptoms of your Niemann-Pick Type C disease?

- Anti-cataplexy/narcolepsy medications
- Antiepileptic (anti-seizure) medications
- Arimoclomol
- Behavioral medications (antidepressants, antipsychotics)
- Cyclodextrin (2-hydroxypropyl- $\beta$ -cyclodextrin)
- Liver X receptor (LXR) and pregnane X receptor (PXR) agonists
- Miglustat/Zavesca/Brazaves
- Neurosteroids e.g., allopregnanolone
- Sleep medications
- Tone medications/botox

- Vorinostat (histone deacetylase (HDAC) inhibitor)

31. Have you ever used any of the following devices as a result of the symptoms of your Niemann-Pick Type C disease?

- Ankle Foot Orthosis (AFO) brace
- Cough assist machine
- Gate supporter or walker
- Gastrostomy tube (G-tube)
- Pulmonary vest
- Tablet / laptop to support speech communication
- Wheelchair

32. What type of doctor or other healthcare provider do you see for your Niemann-Pick Type C disease?

Select as many as apply.

- Acupuncturist
- Chiropractor
- Gastroenterologist
- Homeopathic healthcare provider
- Neurologist
- Pediatrician / internist
- Physical therapist
- Pulmonologist
- Speech therapist
- Other (please specify)

33. How many hours per week do you spend actively managing the disease (e.g., at medical appointments (including travel to and from), physical or occupational therapy, other home-based therapies).

- 0-5 hours
- 5-10 hours
- 10-15 hours
- More than 15 hours

34. Caregiver perspective only (please skip if you are a person with Niemann-Pick Type C disease). How many hours per week do you spend actively managing your child's Niemann-Pick Type C disease (e.g., at medical appointments (including travel to and from), physical or occupational therapy, other home-based therapies).

- 0-5 hours
- 5-10 hours
- 10-15 hours
- More than 15 hours

35. When considering a new treatment for Niemann-Pick Type C disease, which ONE benefit would you consider to be most meaningful?

- Longer life span with same symptoms
- Fewer physical symptoms with same life span



- Fewer neurological symptoms with same life span
- Other (please specify)

36. Caregiver perspective only (please skip if you are a person with Niemann-Pick Type C disease). When considering a new treatment for your child's Niemann-Pick Type C disease, which ONE benefit would you consider to be most meaningful?

- Longer life span with same symptoms
- Fewer physical symptoms with same life span
- Fewer neurological symptoms with same life span
- Other (please specify)

37. Have you ever received a treatment through an expanded access or "compassionate use" program?

- Yes
- No
- Not sure

#### PART VI: CLINICAL TRIALS

38. Have you ever participated in a clinical trial for Niemann-Pick Type C disease?

- Yes
- No

39. (if respondents answer "Yes" to question 38) What type of clinical trial(s) have you been in?

- Observational – observational trials assess health outcomes. Participants continue their regular medical care and are not assigned to specific interventions or investigational treatments. Example: a natural history study.
- Interventional – in an interventional trial, participants receive specific interventions. These interventions may be medical products, such as drugs or devices; procedures; or changes to participants' behavior, such as diet.
- Not sure

40. (if respondents answer "Yes" to question 38) What was the main reason you participated in the clinical trial?

- Desire to advance research
- Desire to help others with Niemann-Pick Type C disease
- Lack of treatment options
- Suggested by my doctor
- Suggested by another person whose family is impacted by the disease
- Suggested by a Niemann-Pick foundation or advocacy organization
- Other

41. (if respondents answer "Yes" to question 38) Would you consider joining a clinical trial again?

- Yes
- No

42. (if respondents answer "No" to question 38) Have you ever tried to participate in a clinical trial but have not been eligible?

- Yes
- No

43. (if respondents answer "No" to question 38) Would you consider joining a clinical trial?

- Yes
- No

44. If you had to decide whether to participate in a clinical trial, how much would these things matter to you?

	A lot	A moderate amount	A little
How long it will take to get to the trial site / how many times you have to go	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
How long the study lasts	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Possibility of receiving the new treatment vs. a placebo or a current treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Whether the treatment could improve my quality of life	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Whether the trial requirements (protocol) are difficult or easy to follow	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Whether there might be negative side effects of the treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Thank You

We appreciate you taking the time to complete this survey. Your answers will help us to gather the information we need to better advance drug development for Niemann-Pick Type C disease.

We hope you are interested in joining the Niemann-Pick Type C PFDD Meeting on Monday, March 18, 2019 in person in Hyattsville, Maryland or via the live webcast. If you indicated that you are interested in speaking on a panel, we will let you know if you have been selected for that role by early February.

For more information on this meeting, including how to register to attend, please visit [niemannpickc-pfdd.com/](http://niemannpickc-pfdd.com/).

## APPENDIX 5: Post-Meeting Survey Addendum Questions

### Survey for NPC Benefit-Risk Calibration for Potential Treatments

\*indicates a required question

#### Introduction and Consent

Welcome to the Niemann-Pick Type C disease patient-focused drug development (PFDD) survey addendum. As with the original PFDD survey, the purpose of this survey addendum is to collect information on people's experiences living with Niemann-Pick Type C disease including their symptoms, treatments, and the impact of the disease on daily life.

This initiative is being organized by the Ara Parseghian Medical Research Fund. The data from this survey, along with the data from the original Niemann-Pick Type C PFDD survey and content presented and discussed at the Niemann-Pick Type C PFDD Meeting on March 18, 2019, will be used to inform the development of a report that will be submitted to the U.S. Food and Drug Administration. Your responses—without your personally identifiable information—may be used for these purposes and/or shared with the Ara Parseghian Medical Research Fund's partners in the PFDD initiative.

This survey is intended for parents and current and past caregivers of those with Niemann-Pick Type C. For parents/caregivers of older children or adults with Niemann-Pick Type C who are involved in their treatment decisions, you may consult with your child when responding if you would like to do so.

Your participation in this survey is optional and if you start the survey, you can stop at any time. If you have questions or concerns about the survey, please contact the Ara Parseghian Medical Research Fund at skassen@nd.edu.

To view the full informed consent, please click [here](#).

1. \*By selecting "I consent" below, you voluntarily agree to participate in this study. [Respondents who select "I do not consent" will be taken to the disqualification page]
- I consent
  - I do not consent

#### Screening Questions

2. \*Are you 18 years of age or older? [Respondents who select "No" will be taken to the disqualification page]
- Yes
  - No

3. \*Do you live in the United States? [Respondents who select "No" will be taken to the disqualification page]

- Yes
- No

4. \*Taking this survey is your choice. You can stop taking the survey at any time. If you agree to participate, please select 'Yes'. If not, click select 'No'.

- Yes
- No

#### Part I: Contact and Background Questions

5. \*Your first and last name: \_\_\_\_\_

6.\*Your phone number and/or email address

- Phone number: \_\_\_\_\_
- Email address: \_\_\_\_\_

7. \*Please enter your ZIP/postal code. \_\_\_\_\_

8. \*What is your year of birth? \_\_\_\_\_

9. \*Which is true about you? I am the \_\_\_\_\_ of the person(s) with NPC.

- Biological father
- Biological mother
- Adoptive father
- Adoptive mother
- Grandmother who is a guardian
- Grandfather who is a guardian
- Other. Please describe: \_\_\_\_\_

10. \*What is your marital status?

- Single
- Married or long-term committed relationship
- Divorced or separated
- Widowed

11. \*Which of the following ethnicities best describes you?

- Hispanic or Latino
- Not Hispanic or Latino

12. \*Which of the following racial groups best describes you? Select all that apply.

- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or Other Pacific Islander
- White
- Other

## Part II: About Your Health

Please answer these questions about your own health.

13. In general, would you say your health is \_\_\_\_\_
- Excellent
  - Very good
  - Good
  - Fair
  - Poor
  - Very poor
14. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? [Yes/No]
- Accomplished less than you would like
  - Were limited in the kind of work or other activities you could do
15. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? [Yes/No]
- Accomplished less than you would like
  - Did work or other activities less carefully than usual
16. During the past 4 weeks, how much of the time have your physical health or emotional problems interfered with your social activities, e.g., visiting or spending time with friends and relatives?
- All of the time
  - Most of the time
  - Some of the time
  - A little of the time
  - None of the time

## Part III: How You Feel About Risk

17. Please rate how you feel about each of the following statements.
- 1 – Strongly agree
  - 2 – Agree
  - 3 – Neutral
  - 4 – Disagree
  - 5 – Strongly disagree

[order of options below randomized for each respondent]

- I enjoy taking risks
  - I avoid situations with uncertain outcomes
  - Taking risks does not bother me if the gains involved are high
  - I consider security an important element in every aspect of my life
  - People have told me that I seem to enjoy taking chances
  - I rarely take risks when there is another alternative
18. Select all of the options that apply to your views. [order of options randomized for each respondent]
- In terms of my expectations in everyday life situations, I am very easy going
  - I expect lots of help and understanding from family and friends on health matters
  - I am demanding of others for general life matters unrelated to health care
  - I expect a lot of myself when it comes to the care of my child(ren)
  - I expect much of myself when it comes to general life matters (beyond child care)

## Part IV: About your Child(dren) with Niemann-Pick Type C

19. How many children with Niemann-Pick Type C do you have?
- One child
  - Two children
  - Three or more children
20. Are all of your children with Niemann-Pick Type C still living?
- Yes
  - No
21. [for people who answer “No” to previous question] In what year(s) did your child(ren) pass away?
- [For people who have two or more children with Niemann-Pick Type C]. If yes, please answer all of the questions in this section thinking about your oldest living child with Niemann-Pick Type C. If none of your children with Niemann-Pick Type C are living, please answer the questions in this section thinking about your child who passed away most recently.
22. In what year was your child with NPC born? \_\_\_\_\_
23. Does the person with NPC currently live in your home?
- Yes
  - No
24. If no, where do they live? \_\_\_\_\_
25. Choose the option that best describes your child’s ambulation or walking abilities today. If you have more than one child with NPC, please answer this question about your oldest living child. If none of your children with NPC are living, please answer the questions in this section thinking about your child who passed away most recently at the time of their passing. Every child is unique and may not

match the descriptions perfectly. Please select the answer that is the best fit. My child with NPC usually:

- a. Is a baby, toddler, or very young child who is too young to walk far yet
- b. Walks independently for long distances outdoors (more than 1/2 mile)
- c. Walks independently outdoors for short distances (such as to the car)
- d. Walks outdoors with help from a person
- e. Walks independently but needs a cane, walker, or other gait supporter outdoors
- f. Walks independently but needs a cane, walker, or other gait supporter both indoors and outdoors
- g. Walks indoors with help from a person and requires a wheelchair outdoors
- h. Uses a wheelchair both indoors and outdoors
- i. Is not mobile / remains in bed or a fixed chair

26. Choose the option that best describes your child's eating and drinking abilities today. If you have more than one child with NPC, please answer this question about your oldest living child. If none of your children with NPC are living, please answer the questions in this section thinking about your child who passed away most recently at the time of their passing. Every child is unique and may not match the descriptions perfectly. Please select the answer that is the best fit. My child with NPC usually:

- a. Eats and drinks with no difficulty
- b. Eats with no difficulty but sometimes has trouble drinking
- c. Eats with no difficulty but consistently has trouble drinking
- d. Sometimes has trouble both eating and drinking
- e. Consistently has trouble eating and drinking
- f. Is unable to safely eat or drink. Requires use of a feeding or gastronomy tube for nutrition

27. Choose the option that best describes your child's speaking abilities today. If you have more than one child with NPC, please answer this question about your oldest living child. If none of your children with NPC are living, please answer the questions in this section thinking about your child who passed away most recently at the time of their passing. Every child is unique and may not match the descriptions perfectly. Please select the answer that is the best fit. My child with NPC usually:

- a. Is a baby who is too young to speak
- b. Is a toddler who cannot always clearly express himself/herself, but knows and uses an age-appropriate number of words.
- c. Uses speech to clearly express himself/herself
- d. Uses speech to express himself or herself but can be difficult to understand.
- e. Is at an age where he/she should be able to speak but is unable to express himself or herself verbally.

28. Niemann-Pick Type C is categorized by different ages of onset. These ages of onset refer to major disease symptoms (such as cognitive delays or ambulation/walking challenges), even though some symptoms may present earlier (such as jaundice or enlarged spleen at birth). Please select the option that best describes your child's NPC.

- a. Early infantile form / Visceral-neurodegenerative (typical onset at <2 years old)

- b. Late infantile form / Neurodegenerative (typical onset between 2 and 6 years old)
- c. Juvenile form / Neurodegenerative (typical onset between 6 and 15 years old)
- d. Adult form / Psychiatric-neurodegenerative (typical onset at >15 years)

29. How much time passed between when your child's NPC symptoms started and when they were officially diagnosed?

- a. Less than 6 months
- b. 6-12 months
- c. 1-2 years
- d. 3-5 years
- e. 6-10 years
- f. More than 10 years

30. Has your child had genetic testing to diagnose NPC?

- a. Yes
- b. No

31. Please rank how much the following symptoms impact daily life for your child with NPC and you using a rank of 1 for greatest impact and 12 for least impact. If your child does not experience

	Child with NPC	You
Ambulation / walking Issues		
Cataplexy		
Cognitive impairment		
Difficulty swallowing		
Fine motor skills issues		
Liver disease or liver failure		
Psychiatric problems (depression/sadness, disorientation, other)		
Respiratory disease / breathing problems		
Seizures		
Sleep disturbances		
Speech problems		
Vertical gaze palsy / eye movement issues		

all of these symptoms, please only rank those they do experience (beginning with 1).

32. Has your child ever experienced a life-threatening emergency as a result of Niemann-Pick Type C that required them to be hospitalized?

- c. Yes
- d. No

33. [If yes to question above] During that life-threatening emergency, were you concerned that your child might die?

- e. Yes
- f. No

34. How much do Niemann-Pick Type C symptoms impact your child's life on the best days? A rank of 5 is the greatest negative impact and a rank of 1 is the least impact.

35. How much do Niemann-Pick Type C symptoms impact your child's life on the worst days? A rank of 5 is the greatest negative impact and a rank of 1 is the least impact.

36. What one symptom has the greatest impact on the worst days? \_\_\_\_\_

37. Please rank how NPC impacts your child's ability to complete the following activities of daily living with 1 being the activity most impacted and 8 being the activity least impacted. If any of these do not apply to your child, such as a young child who does not attend school, please only

Symptom	Rank
Eating/drinking	
Exercise/participation in sports or physical activities	
Household chores/activities	
Personal care (dressing, bathing, toileting)	
School/work performance	
Social activities	
Travel	

rank relevant symptoms beginning with 1.

**Part V: Questions about Treatments**

If you have more than one child with Niemann-Pick Type C, please answer the questions in this section about your oldest living child. If none of your children with Niemann-Pick Type C are living, please answer the questions in this section about your child who passed away most recently at the time of their passing.

38. Please indicate whether your child is using or has previously used any of the following medications or experimental drugs to manage the symptoms of your Niemann-Pick Type C disease?

	Currently Using	Previously Used
Allopregnanolone		
Anti-cataplexy medications		
Antidepressants		
Antipsychotics		
Antiseizure medications		
Arimocloamol		
Botox		
Cyclodextrin (intravenous administration)		
Cyclodextrin (intrathecal administration)		
Miglustat		
Neurosteroids		
Sleep aids		
Vorinostat		

39. Please indicate whether your child is using or has previously used any of the following devices as a result of symptoms of Niemann-Pick Type C.

	Currently Using	Previously Used
Ankle Foot Orthosis (AFO) Brace		
Cough assist machine/vest		
Gait supporter or walker		
Gastronomy tube		
Hearing aid		
Oxygen		
Pulmonary vest		
Tablet / laptop to support speech communication		
Wheelchair		

**Part VI: Your Priorities for Treating NPC**

40. When thinking about the effects of a potential treatment, which of the following activities of daily living would you find most important for your child with NPC to maintain or restore?

- i. Eating/drinking
- j. Exercise or participation in sports/physical activities
- k. Personal care such as dressing, bathing, using the toilet
- l. School or work performance
- m. Social activities

41. Imagine three hypothetical treatments for NPC. Each of these treatments offers one specific benefit: 1) fewer neurological symptoms with same life span, 2) fewer physical symptoms with same life span, or 3) five extra years of life with same symptoms. If you could give your child one treatment, which would you choose? You cannot give your child multiple treatments.

- a. The treatment for fewer neurological symptoms with same life span
- b. The treatment for fewer physical symptoms with same life span
- c. The treatment for five extra years of life with same symptoms

42. Consider a hypothetical treatment that would stop the progression of major symptoms of Niemann-Pick Type C (such as difficulty walking, cognition challenges, and eating/drinking difficulties). If the treatment would only work for a certain percentage of patients, would you be willing to try it? For in the table below, please click the radio button if you would be willing to have your child try an FDA-approved treatment or an experimental treatment if it would stop the progression of symptoms in that percentage of people.

	Currently Using	Previously Used
Ankle Foot Orthosis (AFO) Brace		
Cough assist machine/vest		
Gait supporter or walker		
Gastronomy tube		
Hearing aid		
Oxygen		
Pulmonary vest		
Tablet / laptop to support speech communication		
Wheelchair		

43. Consider a hypothetical treatment that would slow, but not stop, the progression of major symptoms of Niemann-Pick Type C (such as difficulty walking, cognition challenges, and eating drinking difficulties). If the treatment would only work for a certain percentage of patients, would you be willing to try it? For in the table below, please click the radio button if you would be willing to have your child try an FDA-approved treatment or an experimental treatment if it would stop the progression of symptoms in that percentage of people.

	FDA-Approved Treatment	Experimental Treatment
Slow symptom progression in 75-100% of patients		
Slow symptom progression in 50-74% of patients		
Slow symptom progression in 25-49% of patients		
Slow symptom progression in 10-24% of patients		
Slow symptom progression in <10% of patients		

44. Consider the following benefits and risks of potential treatments for NPC. For each section of the table, indicate whether you would be willing to have your child use a treatment that offered that combination of benefit and risk by selecting that option. For example, if you would be willing to have your child use a treatment that would cause them to have fewer neurological symptoms of NPC while putting them at risk of having rare but serious side effects, click the checkbox in that section of the table.

	Common but less serious side effects	Rare but serious side effects (debilitating but not fatal)	Rare but potentially fatal side effects
Fewer neurological symptoms (or slower progression of current symptoms) with same life span			
Fewer physical symptoms (or slower progression of current symptoms) with same life span			
Longer life span with same symptoms			

45. How much would the following considerations impact your decision to have your child try either FDA-approved treatments or experimental treatments? 1 = little impact on my decision, 5 = major impact on my decision.

	FDA-Approved Treatment	Experimental Treatment
Chance of rare but serious side effects		
Chance of rare but fatal side effects		
Chance of common but less serious side effects		
Cost of treatment		
Frequency of treatment		
Potential to slow disease progression		
Potential to stop disease progression		
Potential to reverse prior function loss		

46. If you were asked to have your child join a clinical trial where up to half of the participants would not be receiving the experimental treatment (i.e., receiving a placebo) and there is no therapy approved for NPC, would you be willing to have your child participate?

- a. No
- b. Yes, for a one-year trial
- c. Yes, for a two-year trial
- d. Yes, for a three-year trial

47. Would you be willing to have your child join a one-year clinical trial where up to half of the participants would not be receiving the experimental treatment (and would receive the placebo) if doing so would require your child to stop taking another therapy? Select the answer that best describes your view.

- a. No
- b. Yes, for a one-year trial
- c. Yes, for a two-year trial
- d. Yes, for a three-year trial

### Survey Conclusion

We appreciate you taking the time to complete this survey. Your answers will help us to gather the information we need to better advance drug development for Niemann-Pick Type C disease, including by informing the development of a report to be submitted to the U.S. Food and Drug Administration.

To learn more about the Niemann-Pick Type C Patient-Focused Drug Development initiative, please visit [niemannpickc-pfdd.com/](http://niemannpickc-pfdd.com/).

## APPENDIX 6: Summary of Post-Meeting Survey Addendum Results

In order to delve further into discussion points raised at the Niemann-Pick Type C (NPC) Patient-Focused Drug Development (PFDD) meeting on March 18, 2019, the meeting organizers elected to organize a survey addendum that focused on NPC caregivers' priorities for treating the disease, including benefit-risk tradeoffs of potential therapies. This survey was distributed to the NPC community—including individuals who completed the pre-meeting survey—in July 2019 by all of the NPC patient advocacy organizations involved in planning the NPC PFDD meeting. The data collected in this survey are meant to provide additional context for biopharmaceutical companies developing NPC therapies and the U.S. Food and Drug Administration (FDA) as it reviews prospective therapies.

### Demographics

A total of 52 U.S.-based parents or caregivers of people with NPC completed the survey. Given that the majority of living NPC patients are young children and/or are not responsible for making decisions about their medical care, the survey was not designed to be completed by NPC patients. Parents or caregivers of patients with NPC who are involved in their medical care decisions were informed that they had the option of consulting with their child when responding to the survey. The vast majority of respondents are white or Caucasian individuals of non-Hispanic ethnicity. 63.5% are biological mothers, 25.0% are biological fathers, remaining respondents identified as adoptive parents, grandparents who serve as guardians, or other. 80.8% are married or in a long-term committed relationship, 13.4% are divorced or separated, 5.7% are widowed.

### Questions About Caregivers

To gain insight into the respondents' experiences and thought processes, the survey included a series of questions about the parent/caregiver's health and their feelings about risk. Most respondents indicated that they are healthy, with the following breakdowns by specific categories: Excellent (25.0%), Very Good (44.2%), Good (28.9%), and Fair (1.9%). In four weeks prior to taking the survey, some respondents reported impacts of caregiving on their physical or emotional health or their ability to do work or other activities of daily living (ADL). These results are summarized in the table below.

**Table 1: Impact of physical and emotional health on daily life. N = 52**

	Physical	Emotional
Accomplished less than you would like	75.0%	30.8%
Were limited in the kind of work or other activities you could do	21.2%	Not an option
Did work or activities less carefully than usual	Not an option	21.2%

Respondents were also asked how often their physical or emotional problems interfered with social activities such as visiting or spending time with friends and relatives. Although the plurality (34.6%) said this did not occur, 55.8% said that their physical or emotional problems interfered with their social activities "some of the time" or "a little of the time."

To assess how survey respondents feel about risk, they rated a series of statements regarding risk. A rating of 1 indicated that they strongly agree with the statement and a rating of 5 indicated that they strongly disagree. Average ratings are included in the table below.

**Table 2: How respondents feel about each of the following statements. N = 52.**

I consider security an important element in every aspect of my life	1.9
I rarely take risks when there are other alternatives.	2.6
Taking risks does not bother me if the gains involved are high	2.6
I avoid situations with uncertain outcomes	3.0
People have told me that I enjoy taking risks	3.5
I enjoy taking risks	3.6

Respondents also were asked to indicate whether any of a series of statements about general attitudes in life apply to their views. The table below summarizes the number of people who selected each option.

**Table 3: Options that apply to respondents' views. N = 52.**

I expect a lot of myself when it comes to care of my child(ren)	50
I expect much of myself when it comes to general life matters (beyond child care)	45
In terms of my attitude in everyday life situations, I am very easygoing	31
I expect lots of help and understanding from family and friends on health matters	10
I am demanding of others for general life matters unrelated to health care	6

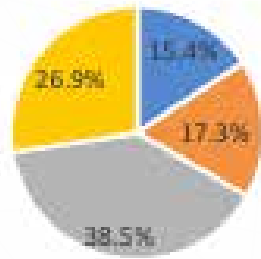
### Questions About People with NPC

Parents/caregivers were asked to answer a series of questions about their child(ren) with NPC. For respondents who have more than one child with NPC, they were asked to answer the questions about their oldest living child. If none of their children with NPC are currently living, they were asked to answer questions about the child who had passed away most recently.

As in the pre-PFDD meeting survey, respondents were asked to choose the option that best describes their child's NPC. As summarized in the graph below, the majority (65.4%) of respondents have children juvenile- or late infantile-onset NPC, which is the most common form of the disease.

Diagram 1: Age of NPC onset. N = 51.

Age of NPC Onset



- Adult form / Psychiatric-neurodegenerative (typical onset at >15 years)
- Early infantile form / Visceral-neurodegenerative (typical onset at <2 years old)
- Juvenile form / Neurodegenerative (typical onset between 6 and 15 years old)
- Late infantile form / Neurodegenerative (typical onset between 2 and 6 years old)

Respondents answered questions about their child’s walking, eating/drinking, and speaking abilities, all of which are impacted by NPC as the disease progresses. Their responses are summarized in the tables below.

Table 4: Options that best describe the walking or ambulation abilities of respondents’ child with NPC. N = 52.

Walking Abilities	Percentage
Walks independently for long distances outdoors (more than ½ mile)	23.1%
Walks indoors with help from a person and requires a wheelchair outdoors	23.1%
Uses a wheelchair both indoors and outdoors	13.5%
Is not mobile / remains in bed or a fixed chair	11.5%
Walks independently outdoors for short distances (such as to the car)	9.6%
Walks independently but needs a cane, walker, or other gait supporter outdoors	9.6%
Walks independently but needs a cane, walker, or other gait supporter both indoors and outdoors	5.8%
Walks outdoors with help from a person	3.8%
Is a baby, toddler, or very young child who is too young to walk far yet	0.0%

Table 5: Options that best describe the eating and drinking abilities of respondents’ child with NPC. N = 52.

Eating/Drinking Abilities	Percentage
Eats and drinks with no difficulty	28.8%
Is unable to safely eat or drink. Requires use of a feeding or gastroonomy tube for nutrition	26.9%
Sometimes has trouble both eating and drinking	21.2%
Eats with no difficulty but sometimes has trouble drinking	13.5%
Consistently has trouble eating and drinking	7.7%
Eats with no difficulty but consistently has trouble drinking	1.9%

Table 6: Options that best describe the speaking abilities of respondents’ child with NPC. N = 52.

Speaking Abilities	Percentage
Uses speech to express himself/herself but can be difficult to understand	40.4%
Uses speech to clearly express himself/herself	30.8%
Is at an age where he/she should be able to speak but is unable to express himself or herself verbally	28.8%
Is a baby who is too young to speak	0.0%
Is a toddler who cannot always clearly express himself/herself, but knows and uses an age-appropriate number of words	0.0%

Respondents were asked to complete a detailed ranking of how much various NPC symptoms impact their child’s daily life and the caregiver respondent’s daily life. The table below shows the average ranking for each option. A ranking of 1 indicates that the symptom has the greatest impact while a ranking of 12 indicates that the symptom has the least impact.

Table 7: Extent to which NPC symptoms impact daily life for child with NPC and respondent. N = 52.

	Child	Parent
Ambulation / walking difficulties	4.0	4.2
Fine motor skills issues	5.2	5.7
Difficulty swallowing	5.2	5.3
Cognitive impairment	5.2	5.4
Speech problems	5.2	4.9
Seizures	5.6	5.4
Respiratory disease / breathing problems	6.0	6.2
Sleep disturbances	6.9	6.9
Vertical gaze palsy / eye movement issues	6.9	6.8
Cataplexy	8.2	8.4
Psychiatric problems (depression/sadness, disorientation, other)	8.4	7.5
Liver disease or liver failure	9.1	9.4

When asked to respond to a free-text question about the one NPC symptom that has the greatest impact on the child’s worst days, the plurality (about one third) of respondents cited challenges with ambulation and balance as a result of cataplexy and lack of muscle tone. Other frequently mentioned symptoms that have a significant impact on ADL were seizures, respiratory challenges, cognition challenges, and difficulty with swallowing.

These responses were consistent with many points raised at the NPC PFDD meeting, when parents and caregivers spoke of their child’s dependence on help for completion of even basic tasks like walking around the house, eating and drinking, or using the restroom. Several meeting participants noted that changes in their child’s ability to walk or run were some of the first NPC symptoms that appeared or were the symptoms that caused them to seek medical assistance.

Half of respondents said that their child had experienced a life-threatening emergency as a result of NPC that led to hospitalization, a data point that highlights the severe nature of this disease. Of those respondents whose children had this experience, 84.6% worried that their child might die during that time.



## Questions About Treatments

As in the pre-PFDD meeting survey, respondents were asked to indicate the therapies (both FDA-approved and experimental) that their child with NPC has used. In this survey, the question also asked respondents to indicate whether the child is currently using the therapy or has previously used the therapy. Please note that 26.9% of respondents were filling out the survey about a child who is deceased, so their child may not have had the option to try therapies that became available in more recent years.

**Table 8: Medications the person with NPC currently uses or has previously used. N = 51.**

	Currently Using	Previously Used
Cyclodextrin (intrathecal administration)	53.8%	3.8%
Miglustat	51.9%	19.2%
Anti-seizure medications	32.7%	9.6%
Sleep aids	15.4%	7.7%
Anti-cataplexy medications	13.5%	3.8%
Cyclodextrin (intravenous administration)	11.5%	3.8%
Botox	7.7%	3.8%
Antidepressants	5.8%	3.8%
Vorinostat	3.8%	3.8%
Antipsychotics	1.9%	5.8%
Arimoclomol	1.9%	0.0%
Allopregnanolone	0.0%	1.9%
Neurosteroids	0.0%	1.9%

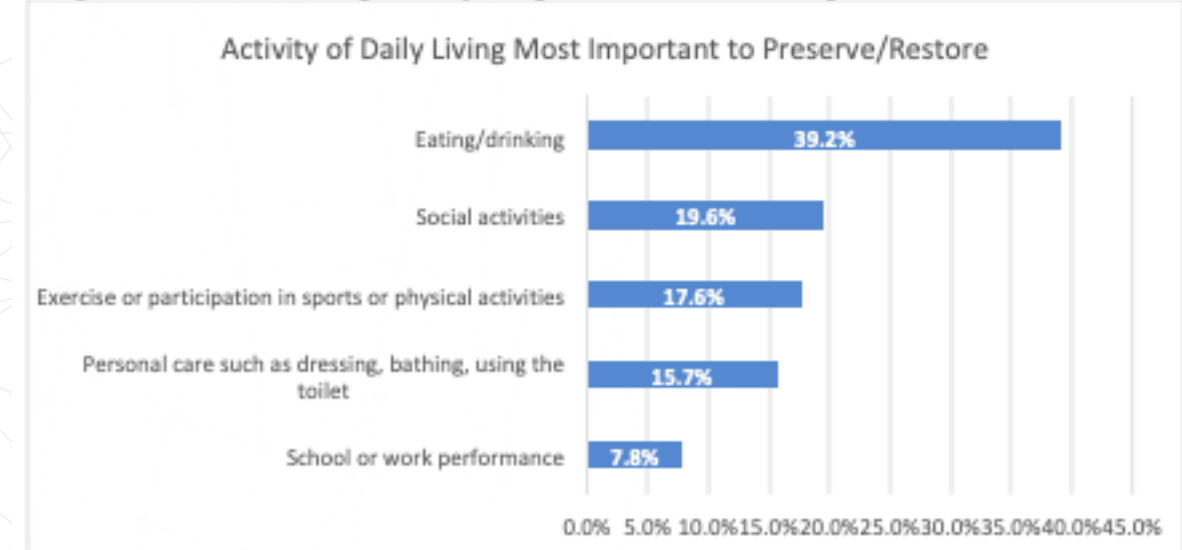
These data highlight the polypharmacy approach that is currently being used to manage symptoms of NPC, as the children of respondents are currently using or have previously used an average of 2.7 different therapies. These data also highlight the extent to which this patient population is exposed to experimental therapies, with just over half of patients having used cyclodextrin administered intrathecally, which is currently in a clinical trial, and Miglustat, which is approved in Europe but not yet approved in the U.S.

## Priorities for Treating NPC

In addition to questions about current approaches to treatment, respondents were asked about their preferences for future treatments for NPC and were presented with multiple hypothetical scenarios. One topic discussed at the PFDD meeting, but not covered explicitly in the pre-PFDD meeting survey, was the activities of daily living that would be most important for a treatment to preserve or restore. The data from this question are summarized in Diagram 2 below.

Interestingly, although respondents indicated in their responses to an earlier question in this survey that walking and ambulation challenges have the biggest impact on their lives and their child's lives, the activity of daily living that they most hope a treatment could preserve or restore is eating/drinking. Parents at the PFDD meeting did note that swallowing difficulties not only make seemingly simple

**Diagram 2: ADL most important for a potential treatment to preserve or restore. N = 51.**

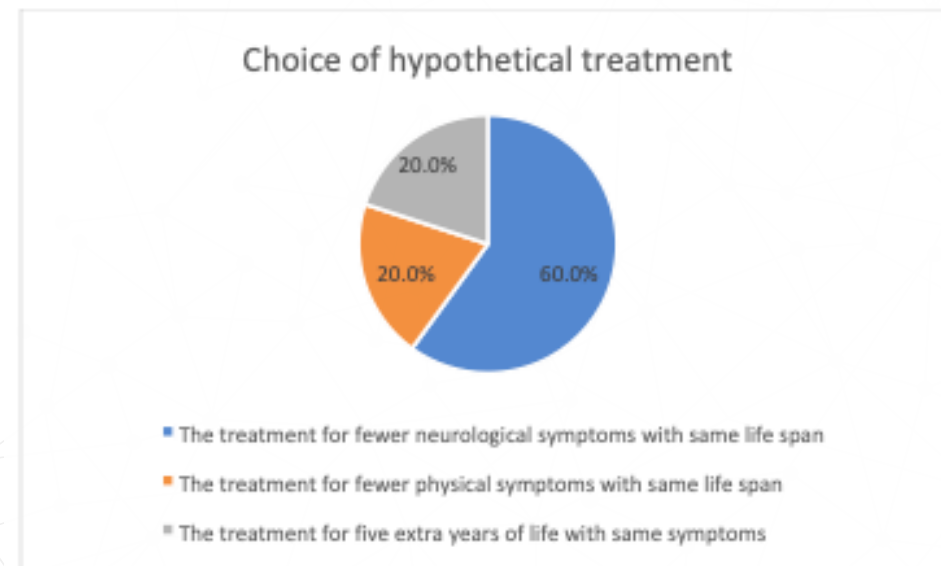


activities like eating or drinking more complicated for patients with NPC, but these activities also can pose a significant health risk. Multiple parents at the PFDD meeting noted that their child developed pneumonia, for which one of the most common causes is aspiration of liquid.

Respondents were asked to envision a scenario in which there were three separate treatments available for NPC, each offering a specific benefit, and patients could only take one of the three treatments. As shown in Diagram 3 below, 60.0% of respondents indicated that they would prefer that their child have the treatment that would reduce neurological symptoms of NPC as opposed to the one that would reduce physical symptoms or the one that would extend the child's lifespan. This is consistent with the comments that many NPC parents and caregivers made at the PFDD meeting when they noted that a positive impact of some treatments they've seen are when a "light comes back" in their child's eyes. Parents noted that even if their child remained unable to walk, parents would be happy if they felt their child was still able to understand and experience what is going on in the world around them.

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**Diagram 3: Preferred treatment for person with NPC if only one of the three listed hypothetical treatments can be used. N = 50.**



The survey also asked respondents questions about their willingness to try a hypothetical FDA-approved or experimental treatment that was only expected to work for a certain percentage of patients. Respondents were asked this question about hypothetical treatments that could either stop progression of major NPC symptoms (e.g., difficulty walking, cognition challenges, and eating/drinking problems) or slow, but not stop, those symptoms. In both cases, respondents indicated that they had a high willingness to try either an FDA-approved or experimental therapy, although they had a somewhat greater willingness to try an experimental therapy that might not work for all patients. This is perhaps not surprising given the fatal nature of NPC and the current lack of treatments or cures and is reinforced by the patient community's extensive exposure to current experimental therapies.

**Table 9: Percentage of survey respondents willing to try a hypothetical treatment that would stop progression of major NPC symptoms but would only work for a certain percentage of patients. N = 50.**

	FDA-Approved	Experimental
75-100% of patients	78.0%	88.0%
50-74% of patients	80.0%	84.0%
25-49% of patients	70.0%	78.0%
10-24% of patients	66.0%	64.0%
<10% of patients	52.0%	42.0%

**Table 10: Percentage of survey respondents willing to try a hypothetical treatment that would slow but not stop progression of major NPC symptoms but would only work for a certain percentage of patients. N = 50.**

	FDA-Approved	Experimental
75-100% of patients	76.0%	88.0%
50-74% of patients	78.0%	82.0%
25-49% of patients	68.0%	76.0%
10-24% of patients	60.0%	60.0%
<10% of patients	48.0%	48.0%

In another question about hypothetical treatments for NPC, respondents were asked to consider whether they would be willing to have their child use treatments that offer different combinations of benefits and risks. As shown in Table 11 below, a large majority of respondents are willing to have their child use a treatment that has common, but less serious, side effects, if it offered any of the three benefits, especially a reduction of the neurological symptoms of NPC. Respondents were less willing to tolerate risks of rare but serious or potentially fatal side effects, although they were more willing to do so if the treatment would improve neurological symptoms.

**Table 11: Respondent selections regarding benefit and risk combinations for hypothetical treatments for NPC. N = 49.**

N = 49	Common but less serious side effects	Rare but serious side effects (debilitating but not fatal)	Rare but potentially fatal side effects
Fewer neurological symptoms (or slower progression of current symptoms) with same life span	87.8%	55.1%	24.5%
Fewer physical symptoms (or slower progression of current symptoms) with same life span	85.7%	51.0%	10.2%
Longer life span with same symptoms	77.6%	38.8%	8.2%

Respondents also answered a question in which they were asked to rate how much various factors would impact their decision to have their child use either an FDA-approved treatment or an experimental therapy. The data, summarized in Table 12 below, showed that survey respondents place the most weight on whether a treatment is likely to reverse prior function loss or stop or slow disease progression and whether it has a chance of rare, but fatal, side effects. The cost or frequency of treatment and the chance of less serious side effects appear to be less important to parents when choosing a treatment. Whether a treatment is approved by the FDA or is experimental did not appear to have a notable impact on how respondents make treatment decisions.

**Table 12: Average rating of likelihood of factors to impact decision to use an FDA-approved treatment or experimental therapy for NPC. 1 = little impact on decision, 5 = major impact on decision. N = 50.**

	FDA-Approved	Experimental
Potential to reverse prior function loss	4.6	4.6
Potential to stop disease progression	4.5	4.5
Chance of rare but fatal side effects	4.4	4.4
Potential to slow disease progression	4.2	4.3
Chance of rare but serious side effects	3.5	3.3
Cost of treatment	2.3	2.2
Chance of common but less serious side effects	2.1	2.2
Frequency of treatment	1.9	2.0

Given the increasing number of NPC therapies in development and clinical trials, the survey included questions about whether respondents would be willing to have their children participate in a trial where up to 50% of participants would receive a placebo. Approximately 60% of respondents indicated that they would be willing to have their child participate in such a trial for one year, but only a small percentage of respondents would be willing to have their child participate in a longer trial. 28.6% of respondents would not be willing to have their child participate in a trial where they have a 50% chance of receiving a placebo.

**Table 13: Willingness to have child participate in a clinical trial where up to 50% of participants will get the placebo. N = 49.**

Yes, for a one-year trial	59.2%
No	28.6%
Yes, for a three-year trial	8.2%
Yes, for a two-year trial	4.1%

As a follow-up question, those who indicated they would be willing to have their child participate in such a trial were asked whether their answer would change if the child had to stop taking another therapy. In this scenario, equal numbers of respondents said they would not participate in such a trial or would only be willing to do so for one year.

**Table 14: Willingness to have child participate in a clinical trial where up to 50% of participants will get the placebo and participants have to stop taking another therapy. N = 36.**

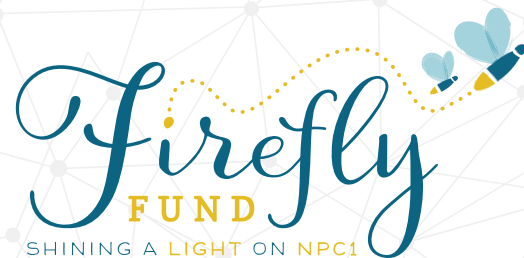
Yes, for a one-year trial	47.2%
No	47.2%
Yes, for a three-year trial	2.8%
Yes, for a two-year trial	2.8%

### Conclusion

The results from this survey addendum provide useful context on NPC caregivers' views regarding priorities, tolerance of uncertainty, and perspectives on benefits and risks of hypothetical treatments for NPC. The majority of respondents would prefer to have a treatment that addresses the neurological impacts of NPC, particularly those with an outward physical manifestation on functions such as ambulation/walking and eating/drinking. The survey data reinforced points made at the PFDD meeting about the NPC community's willingness to try experimental therapies or approved therapies that may only have demonstrated efficacy in a small number of patients. Although they are interested in participating in research, NPC caregivers would be hesitant to have their children participate in longer placebo-controlled trials, particularly if doing so meant they had to cease taking another therapy. Above all, NPC caregivers who completed this survey or participated in the PFDD initiative in some other way desire more and better treatments to slow or stop the progression of—and ultimately, cure—this devastating disease.

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