

RESULTS OF A SURVEY ON PREFERENCES FOR TREATMENTS FOR NIEMANN-PICK TYPE C

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EXECUTIVE SUMMARY

In Fall 2020, the Nieman Pick Type-C (NPC) Therapy Accelerator (NTA) conducted a survey of NPC patients and caregivers to collect information on their experiences with the disease and preferences for future treatments. A total of 59 respondents—38 in the U.S. and 21 from other countries—with all forms of NPC completed the survey. This report presents the initial findings from analysis of the survey data, summaries of which are included below.

- NPC has far-reaching effects on physical and mental abilities of patients. The majority of survey respondents experience a cognitive delay or are losing cognitive skills, have speech challenges, and have limited gross and fine motor skills.
- NPC symptoms result in significant limitations in respondents' abilities to complete activities of daily living such as eating and drinking, social activities, and personal care. Over the last five years, all respondents experienced a decreased ability to carry out these types of activities.
- When thinking of the potential benefits of future treatments, the two benefits respondents are most desirous to see are an improvement or stabilization of cognition and swallowing abilities. When potential treatment benefits were described in terms of activities of daily living, eating and drinking was the activity that respondents most wanted to maintain or restore.
- Nearly half of respondents who rated cognition or swallowing abilities as the most important benefit of a potential treatment would be willing to try such a treatment even if it only works for less than 10 percent of people. If a treatment would work for at least 75 percent of people, 95 percent of respondents would be willing to try it.
- Although respondents have a fairly high tolerance for potential treatment side effects, especially if the treatment could significantly slow the progression of NPC, they are most concerned about serious side effects like aspiration pneumonia and seizures. Either of these side effects would make the majority of respondents (80 percent) stop taking a treatment.
- Of potential side effects included in this survey, the one most likely to be accepted by respondents was hearing loss that could be corrected with a hearing aid.
- Respondents are willing to take treatments through a variety of routes of administration and those requiring frequent visits to doctors' offices and long-distance travel.
- Despite their willingness to tolerate many access challenges in order to try a new treatment, a majority of respondents remain concerned about the potential cost of treatment.

This report and the anonymized data from this survey will be shared with the U.S. Food and Drug Administration (FDA) to help them better understand the priorities of people with NPC and their caregivers. The data will also be made available, upon request, to researchers and pharmaceutical companies for further analysis with the hope that it will help spur development of much-needed new treatments for this devastating disease.

INTRODUCTION

In order to better understand the experiences of people with Niemann-Pick Type C (NPC) and their preferences for future treatments, the NPC Therapy Accelerator (NTA) conducted an online patient and caregiver survey. This survey included questions about NPC symptoms, treatments, the impact of the disease on daily life, and respondents' preferences for benefits and risks of future treatments. This report presents the initial findings from the survey with the aim of helping U.S. Food and Drug Administration staff to better understand the experiences and priorities of people living with NPC and their caregivers.

This survey builds on two previous surveys conducted in connection with the 2019 [NPC patient-focused drug development \(PFDD\) meeting](#). The NTA members, who organized the PFDD meeting along with other advocacy groups and community members, have since created this new initiative to promote collaboration and data sharing among members of the NPC research community including pharmaceutical companies, clinicians, and academic researchers. Data from this survey will be shared with such members of the NPC community upon request to facilitate further analysis including of data from respondents outside the U.S. and more detailed subgroup analyses. Through this survey and other research efforts, the NTA aims to spur innovative research on treatments and, eventually, cures for this devastating disease.

SURVEY DESIGN AND ANALYSIS APPROACH

The 34- question survey was designed in SurveyMonkey and was reviewed and approved by the University of Notre Dame Institutional Review Board (IRB). A link to the survey was distributed by members of the NTA and other NPC patient advocacy organizations via email distribution lists and social media posts. The survey opened on October 29, 2020 and closed on December 7, 2020 (40 days). The survey received 59 complete, unique responses; partial and duplicate responses were not included in the final dataset. Given typical age and cognitive abilities of a person with NPC, the survey was designed to be completed by caregivers, but one patient also completed the survey. For purposes of this report, unless otherwise specified, the term "respondent" refers to both that patient and those patients whose caregivers filled out the survey on their behalf.

RESPONDENT DEMOGRAPHICS

A total of 38 U.S.-based respondents completed the survey. In addition, 21 people from other countries also completed the survey. They included respondents from Canada, Germany, Ireland, the Netherlands, Switzerland, the United Arab Emirates, and the United Kingdom. The fact that survey responses were received from people around the world highlight's the global NPC community's commitment to advancing research on future treatments and cures for this disease.

The sex, ethnicity, and race of the respondents is summarized below in Figures 1-3. Most of the respondents (78.9 percent) are current caregivers, but former caregivers of people with NPC who have passed away also completed the survey (21.1 percent). The average age of the current patients represented in this survey data is 21 years.

Fig 1: Sex of Respondents (n=38)

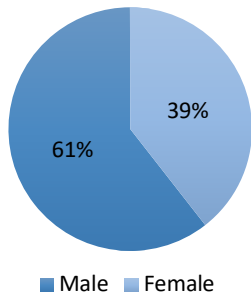


Fig. 2: Ethnicity of Respondents (n=38)

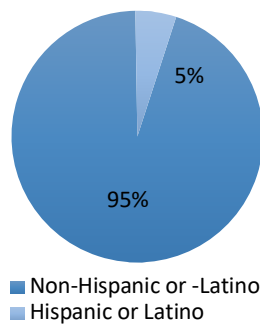
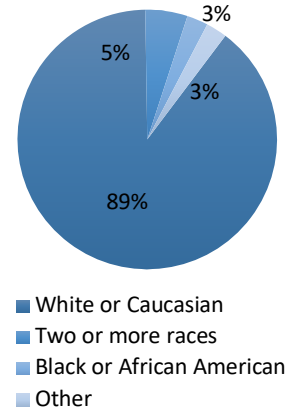


Fig. 3: Race of Respondents (n=38)



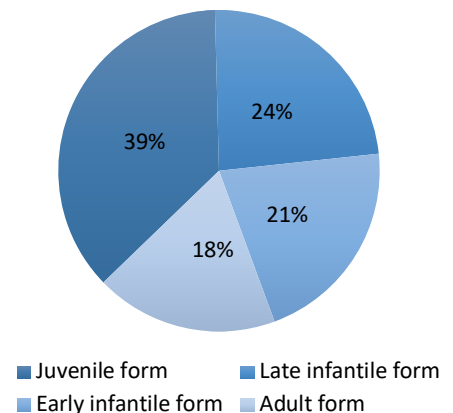
CURRENT DISEASE STATE AND SYMPTOMS

NPC is often characterized by the age of the patient at the time when their symptoms appear. Although most people begin to exhibit symptoms in early childhood, some people may not have symptoms until they are adults. For purposes of this survey, the ages of onset/diagnosis were defined as follows:

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

As shown in Figure 4, the juvenile or “classic” form of NPC was most common among survey respondents and there was a fairly equal distribution of people with the other three forms.

Fig. 4: NPC Age of Onset (n=38)



The progression of NPC is often measured using a clinical severity assessment that combines a functional disability scale and a neurocognitive assessment.¹ This assessment includes seven different “domains” with scoring levels for each. For purposes of this survey, respondents were asked about the person with NPC’s abilities across five domains: 1) walking or ambulation abilities, 2) swallowing abilities, 3) fine motor skills, 4) cognitive skills, and 5) speaking abilities. Those responding on behalf of an NPC patient who is no longer living were asked to choose the option that describes that person’s abilities at the time of their passing. These domains were chosen both because of their impact on daily life and because they can be more readily estimated by a non-clinician. The responses to these survey questions are not intended to replace a formal assessment by a clinician, but provide helpful baseline information about the population represented in this survey.

¹ Geberhiwot T, Moro A, Dardis A, et al. Consensus clinical management guidelines for Niemann-Pick disease type C. Orphanet J Rare Dis. 2018;13(1):50. Published 2018 Apr 6. doi:10.1186/s13023-018-0785-7.

As summarized below and shown in Figures 5-9, most patients experience significant impacts from NPC across one or more domains. Of all 38 respondents, only two (5 percent) were reported to experience no notable effects of NPC across any of the five domains.

- **Walking Abilities (Figure 5):** A large majority (77 percent) of respondents have some sort of difficulty walking as a result of their disease. Just over half (55 percent) have significant ambulation challenges and either require a gait supporter or cannot walk at all. Less than one quarter (24 percent) of respondents are able to walk independently without notable ambulation challenges.
- **Swallowing Abilities (Figure 6):** Almost all survey respondents are at one of two extremes in terms of their swallowing abilities: they either have no trouble or very little trouble swallowing (63 percent) or require a feeding tube for all of their nutrition (29 percent). This split is perhaps indicative of a rapid loss of swallowing abilities as NPC progresses.
- **Fine Motor Skills (Figure 7):** Most respondents (79 percent) have some issues with fine motor skills, although the exact degree to which these skills are impacted varies greatly.
- **Cognitive Skills (Figure 8):** Over one third (34 percent) of respondents are losing their cognitive skills as a result of NPC. An additional 45 percent are experiencing some sort of cognitive delay.
- **Speaking Abilities (Figure 9):** A vast majority of people represented in this survey (92 percent) have at least some trouble speaking as a result of NPC. Just over one quarter (27 percent) are unable to communicate verbally.

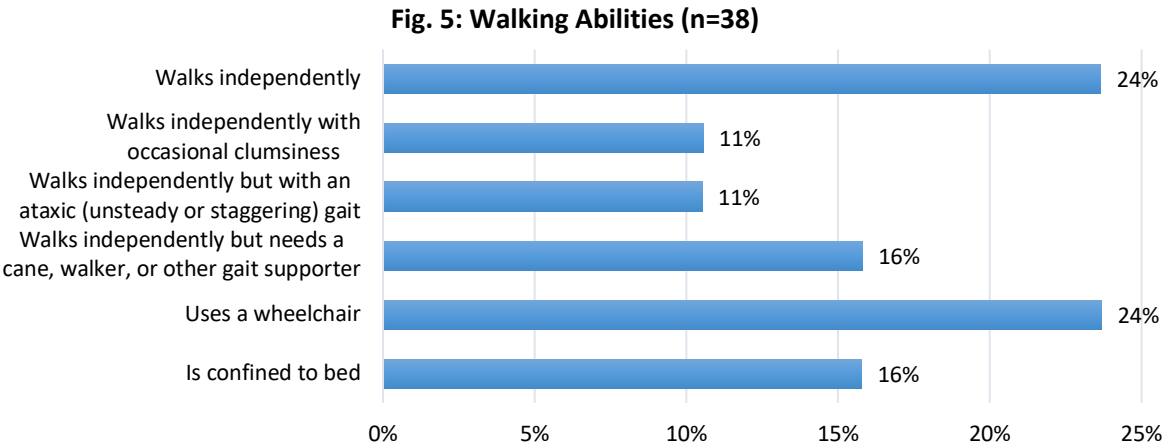


Fig. 6: Swallowing Abilities (n=38)

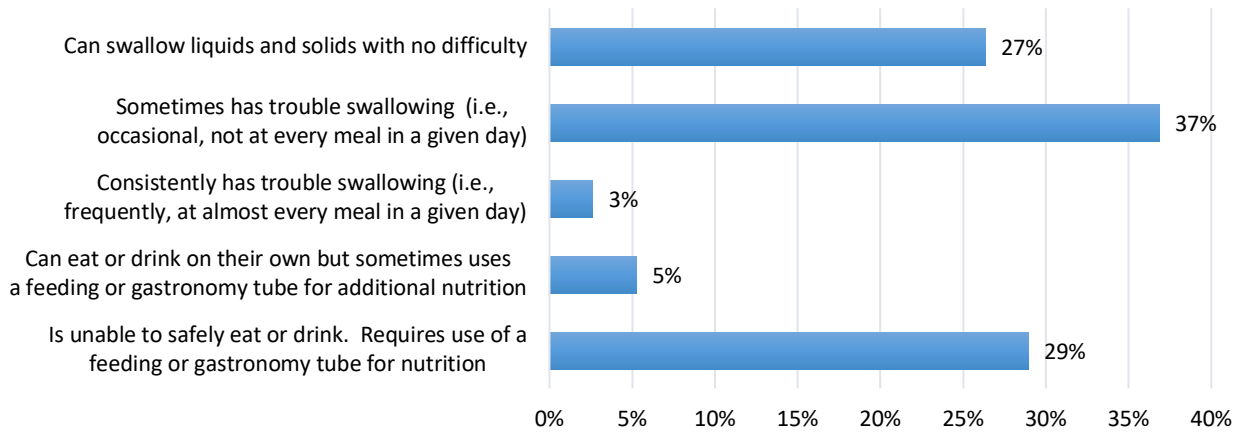


Fig. 7: Fine Motor Skills (n=38)

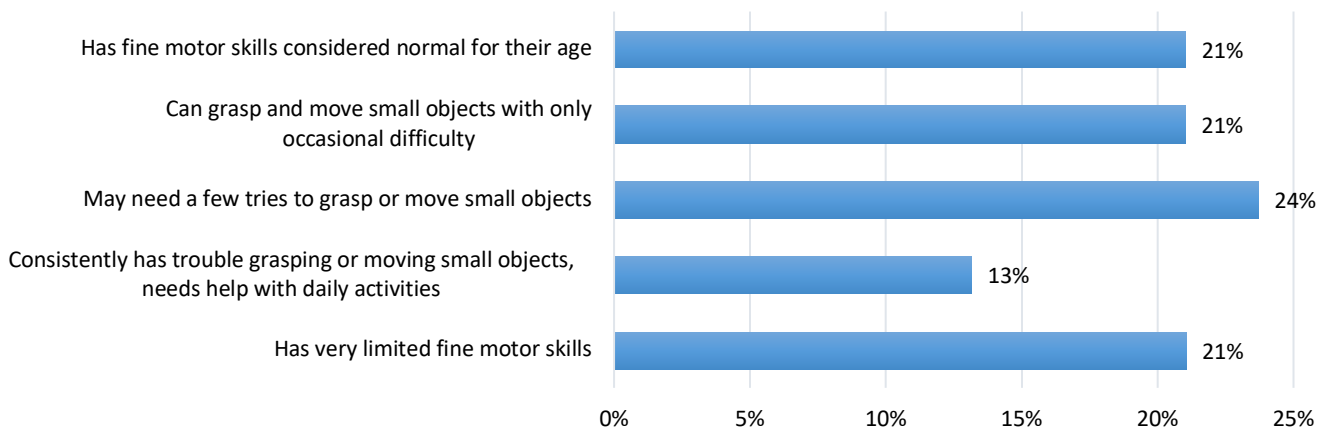


Fig. 8: Cognitive Skills (n=38)

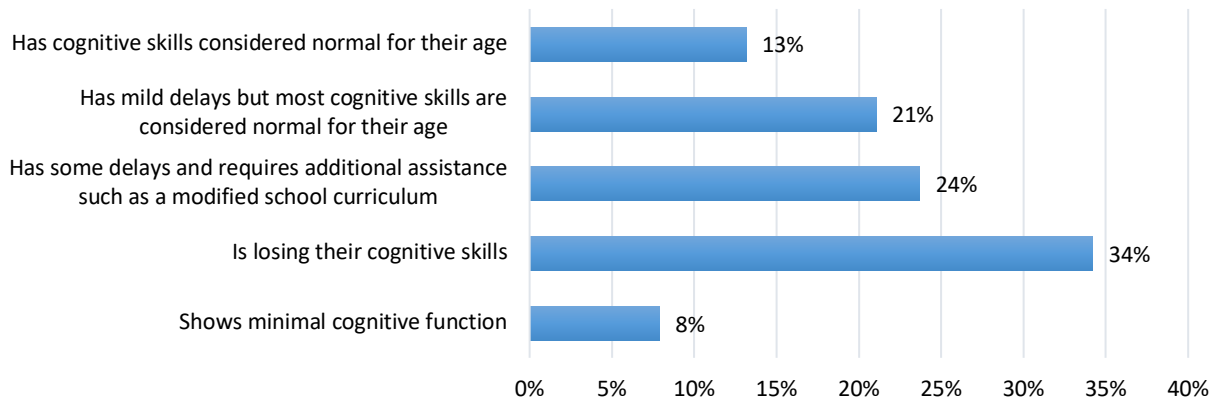
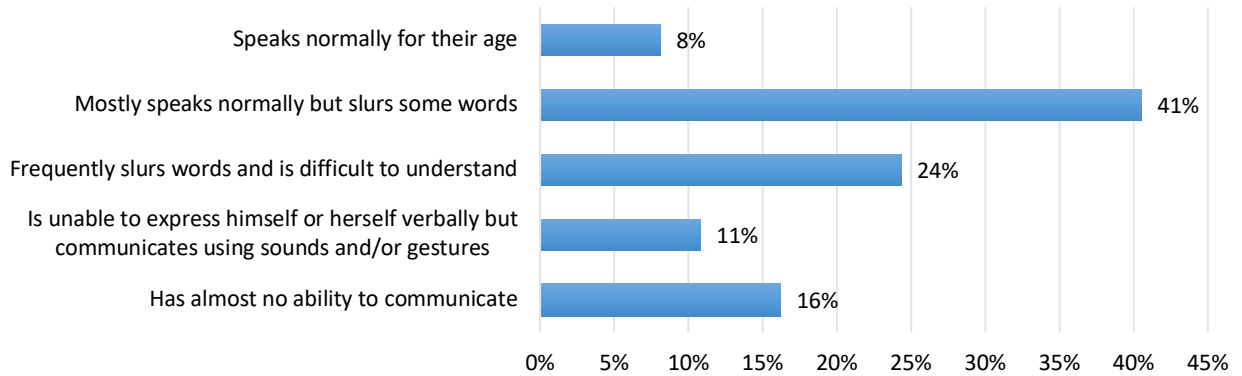
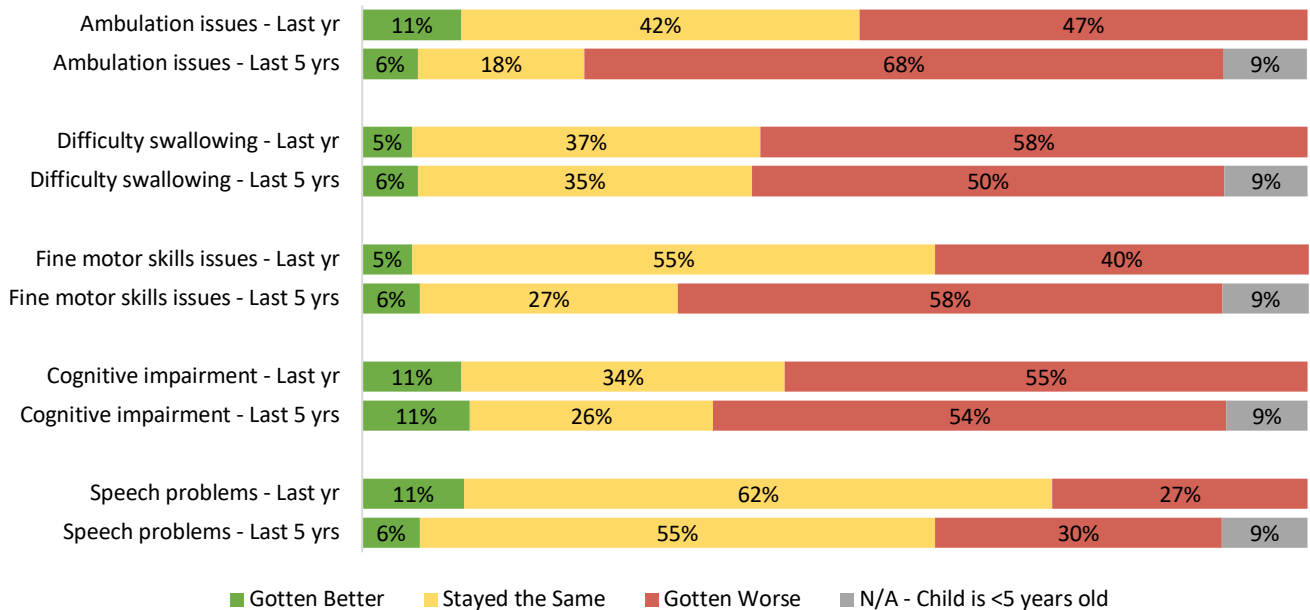


Fig. 9: Speaking Abilities (n=37)



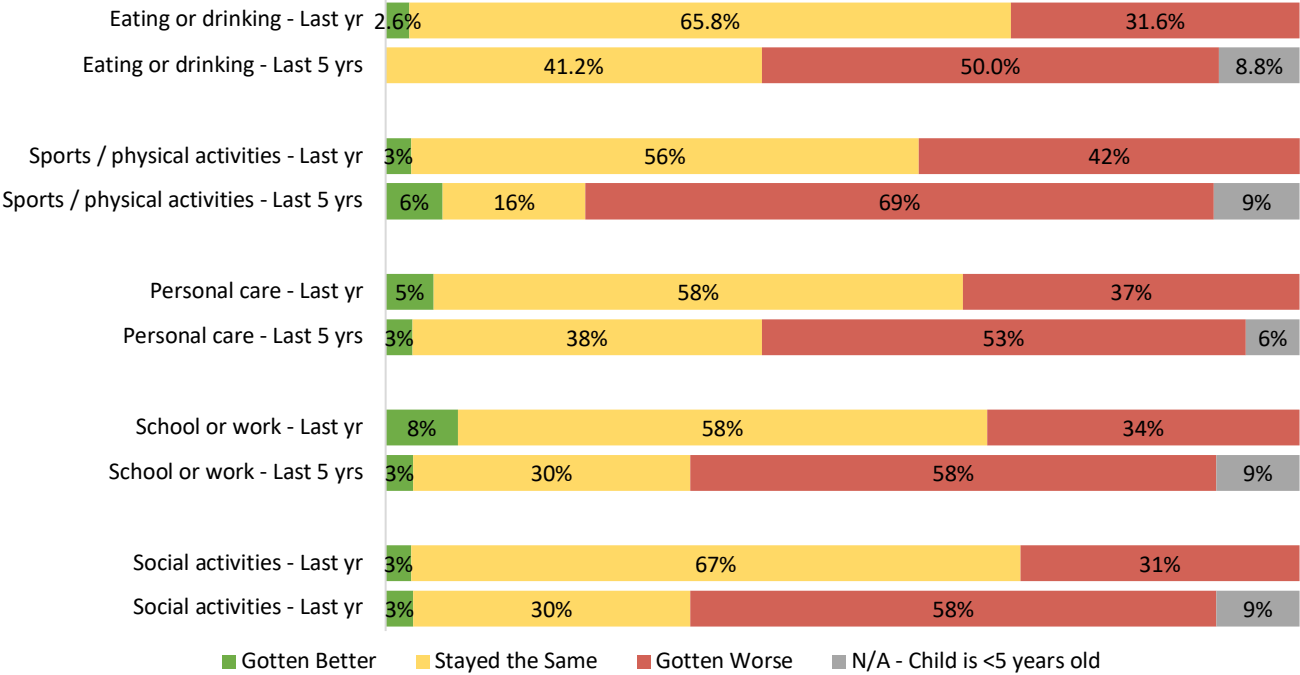
The challenges of NPC symptoms are further highlighted by data showing how patients’ symptoms in each of the five domains have changed over the last year and last five years (Figure 10). For either time period, no more than approximately 10 percent of survey respondents showed significant improvement for any domain. Most experienced no change or a loss in abilities over time. The domains with the biggest differences between disease impacts over the last year and the last five years are ambulation and fine motor skills, for which a significantly higher percentage of respondents reported worsened symptoms over the longer timeframe. When considering potential future treatments for NPC, this data highlights the importance of considering long-term benefits of a treatment.

**Fig. 10: Symptom Progression Over Last Year and Last Five Years
n=33-38 (varies)**



The decline that people with NPC experience over time is even more apparent when considering how the disease impacts patients’ abilities to carry out activities of daily living (ADL). As shown in Figure 11, for all five categories, a majority of respondents said their ability to complete that ADL remained the same over the last year. Over five years, however, a majority of respondents said their ability to complete that activity became worse. Given the small percentage of respondents to experience any improvement in their ability to complete ADL over one or five years, it is reasonable to assume that a potential future treatment that could maintain existing skills would still be seen as an important benefit. The progressive nature of NPC means that symptom improvement over time is unlikely, but a treatment that could prevent worsening, especially over a longer time period, would be significant.

Fig. 11: Change in Ability to Complete ADL over Last Year and Last Five Years
n=32-38 (varies)



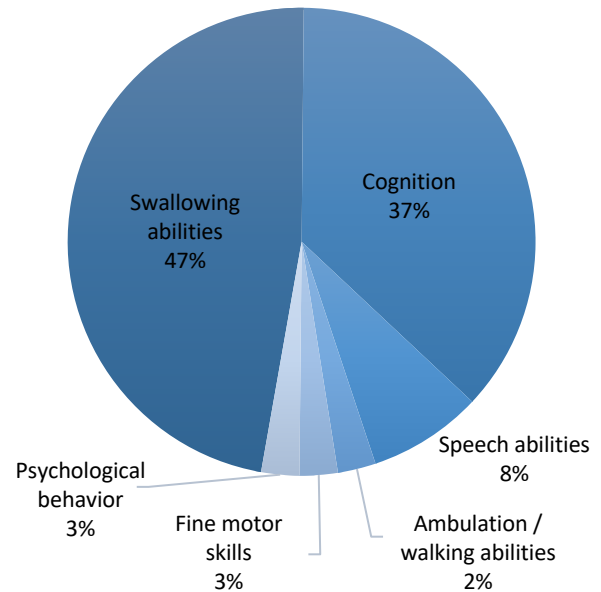
EXPERIENCE WITH TREATMENTS

Although there are very limited treatment options available for NPC, all but three respondents currently take an approved treatment or investigational drug or took one in the last year. Cyclodextrin, an investigational therapy administered either intrathecally (IT) or intravenously (IV), is the most common treatment taken by respondents (61 percent). Of those who take or have taken cyclodextrin, 60 percent use the IT route of administration, 17 percent the IV route of administration, and 26 percent receive both IT and IV treatment. Miglustat (brand name Zavesca), a therapy approved in the U.S. for the treatment of Gaucher disease, is also commonly used to treat NPC: 55 percent of respondents take or have taken this drug. Anti-seizure medications were the next most commonly used treatment, with 45 percent of respondents reporting current or previous use of these drugs. Smaller percentages of respondents take or have taken anti-cataplexy medications, antidepressants, antipsychotics for psychosis, arimocloamol, botox, N-Acetyl-L-Leucine (IB1001), sleep aids, and Vorinostat. Survey respondents take or have taken an average of 2.4 treatments or investigational therapies for their NPC.

PREFERENCES FOR TREATMENT BENEFITS

When considering benefits of potential future treatments, respondents are most desirous to improve or maintain cognition or swallowing abilities. This preference was expressed in response to a question in which respondents could choose only one symptom that could be addressed by a treatment, with all other symptoms continuing to get worse. As shown in Figure 12, nearly half of respondents (47 percent) would choose a treatment that would improve or maintain swallowing abilities and over one third (37 percent) would choose one that would improve or maintain cognition. Given the significant day-to-day challenges associated with declining cognition or ability to swallow (and thus, eat or drink independently), it is perhaps not surprising that these treatment benefits are very important to respondents. Although chosen by fewer respondents, the importance of a treatment that could maintain or improve walking abilities, speech abilities, fine motor skills, or psychological behavior should not be discounted given how much a decline in these areas can also impact quality of life for patients and caregivers.

Fig. 12: Top symptom to improve or maintain (n=38)



Recognizing that the progression of NPC can vary from person to person and that potential new treatments may not be equally effective for all patients, the survey also included a question about respondents' tolerance for uncertainty in a new treatment that might offer their one preferred benefit. For those who prefer the swallowing benefit, about 45 percent are willing to try a new treatment even if only works for less than 10 percent of people. Nearly 30% of those who prefer a treatment to improve or maintain cognition would be willing to try it with that same level of uncertainty. This high tolerance for uncertainty highlights the dire nature of NPC and the significant unmet medical need for this patient population. For a treatment that would work for at least 75 percent of people, almost all of the respondents (95 percent) would be willing to try it.

Table 1: Tolerance for uncertainty in a treatment that could improve or maintain one ability (n=38)

Preferred treatment benefit	75-100%	50-74%	25-49%	10-24%	<10%
Improve or maintain swallowing abilities	18/18 (100%)	18/18 (100%)	17/18 (94%)	13/18 (72%)	8/18 (44%)
Improve or maintain cognition	14/14 (100%)	13/14 (93%)	12/14 (86%)	7/14 (50%)	4/14 (29%)
Improve or maintain speech abilities	2/3 (67%)	2/3 (67%)	1/3 (33%)	1/3 (33%)	1/3 (33%)
Improve or maintain ambulation/walking abilities	1/1 (100%)	1/1 (100%)	1/1 (100%)	0/1 (0%)	0/1 (0%)
Improve or maintain fine motor skills	1/1 (100%)	1/1 (100%)	1/1 (100%)	0/1 (0%)	0/1 (0%)
Improve psychological behavior	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)

The preferences for treatment benefits regarding symptoms are mirrored in the responses to a similar question about the ADL respondents would most prefer to maintain or restore. As shown in Figure 13, a majority of respondents—55 percent, more than triple the next highest choice—would prefer a treatment that could maintain or restore eating and drinking abilities. The next most commonly chosen benefit is maintaining or restoring the person with NPC’s ability to participate in social activities.

The results of these questions align with comments made by members of the NPC community during the 2019 PFDD meeting. Parents of children with NPC spoke of their hopes for a treatment that would bring the light back into their children’s eyes and make it clear that their child was still interested in and aware of the world around them. Others spoke of their children’s disappointment at no longer being able to safely eat favorite foods and the challenges of using a feeding tube when a child repeatedly tries to pull it out. Quotes from meeting participants are included below.

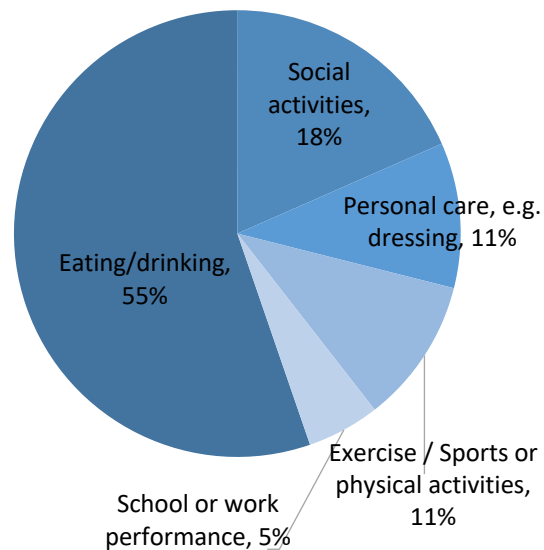
- “What is most meaningful to us right now with her is swallowing. We live in fear of pneumonia... of choking from not only eating the food but just choking on saliva at night when she’s sleeping.”
- “We were told that his body was storing cholesterol and so we put him on a cholesterol lowering regimen...if I could...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.”
- “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 progression of NPC symptoms eventually limits a person’s ability to walk, manage their personal care, or participate in typical activities like work or school. When faced with a choice of potential treatment benefits, however, respondents seem more willing to accept these difficulties as long as the person with NPC continues to be able to eat and drink on their own and maintains their cognition and thus, their personhood.

TOLERANCE FOR SIDE EFFECTS

When considering future treatments for NPC, survey respondents also demonstrated a fairly high tolerance for side effects, including those that are long-term, of a treatment that could slow the progression of NPC even a small amount. Respondents were asked about their willingness to tolerate side effects of three hypothetical treatments for NPC that would slow disease progression slightly (by up to one year compared to no treatment), moderately (by three to five years), or significantly (by eight to ten years). For any of these hypothetical treatments, the side effects of greatest concern were vomiting, fevers, diarrhea, and back pain. Of all of the possible side effects, the one respondents were most likely to tolerate over the long term was hearing loss that

Fig. 13: Top ADL to maintain or restore (n=38)



could be corrected with a hearing aid. For a treatment that could significantly slow the progression of NPC, more than half of respondents would also be willing to tolerate long-term fatigue, ataxia, and back pain. In general, the more of an effect a treatment was likely to have on the progression of NPC, the more likely respondents were to tolerate more types of side effects over a longer period of time. See Figures 14-16 for additional detail.

Fig. 14: Willingness to tolerate side effects of a treatment to slightly slow NPC progression (n=38)

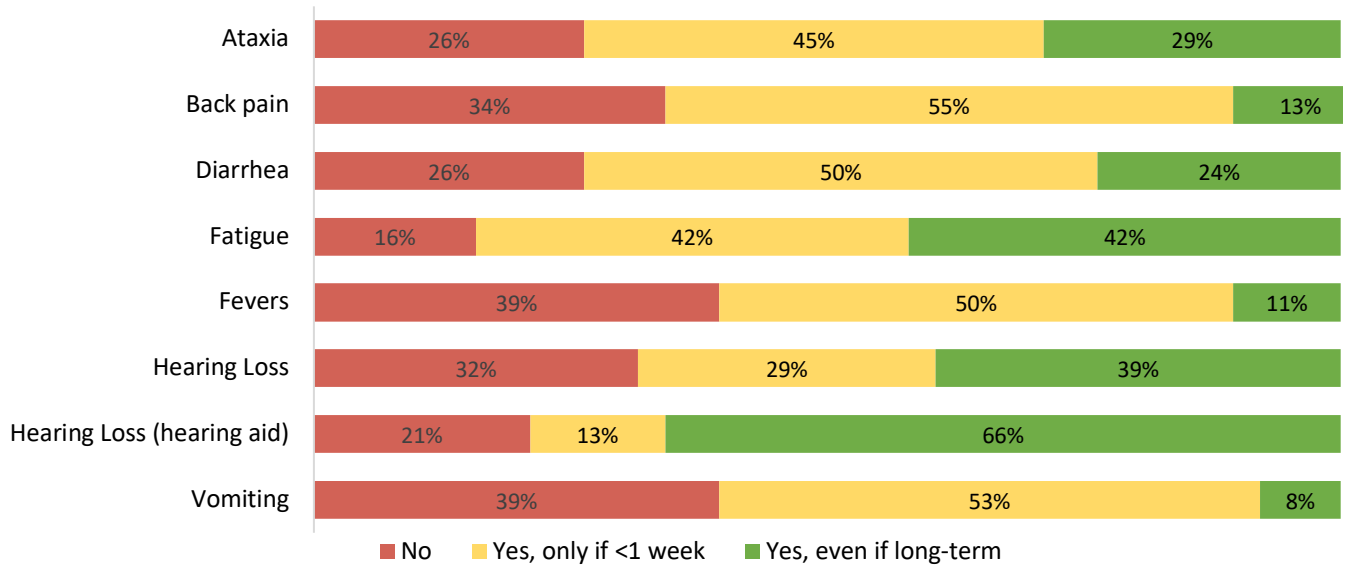


Fig. 15: Willingness to tolerate side effects of a treatment to moderately slow NPC progression (n=38)

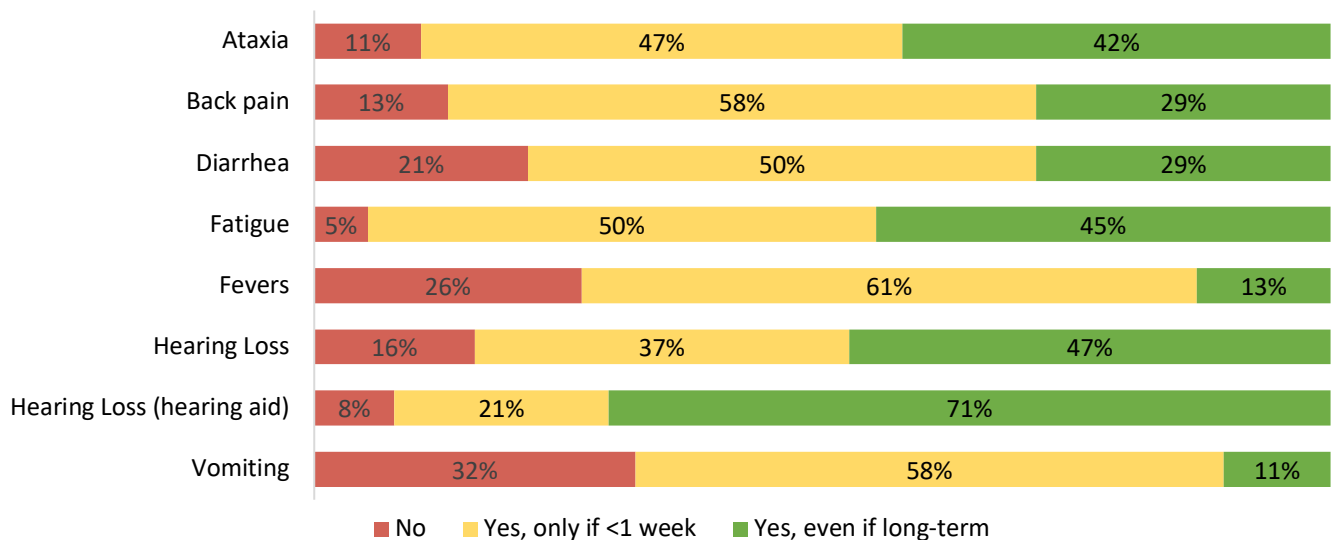
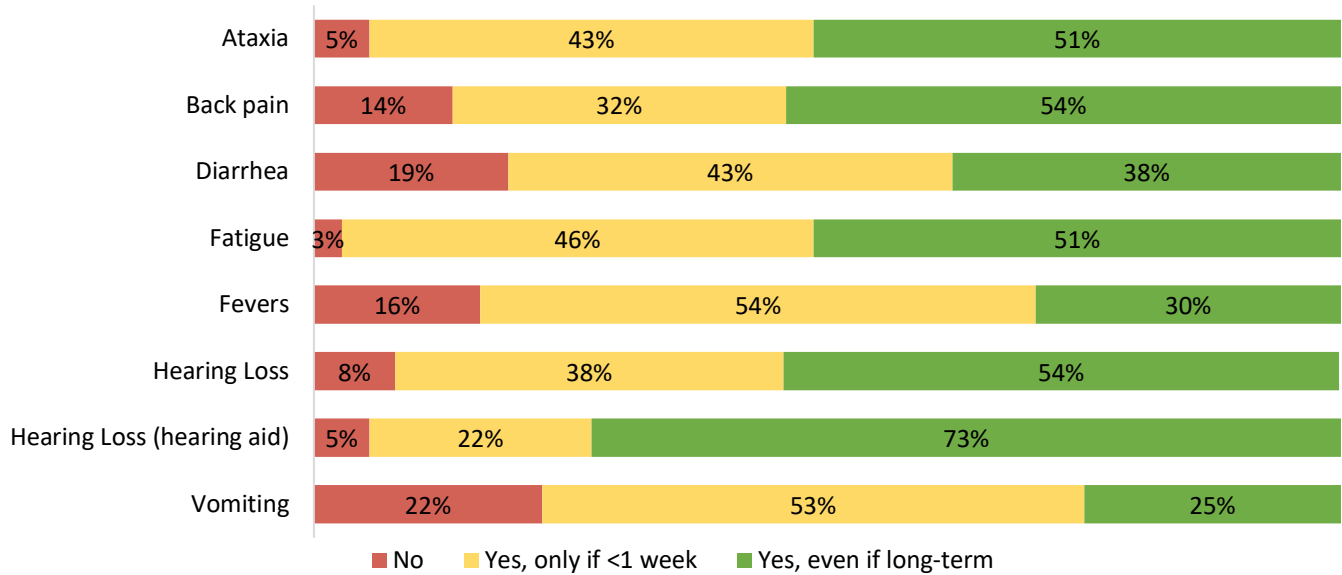
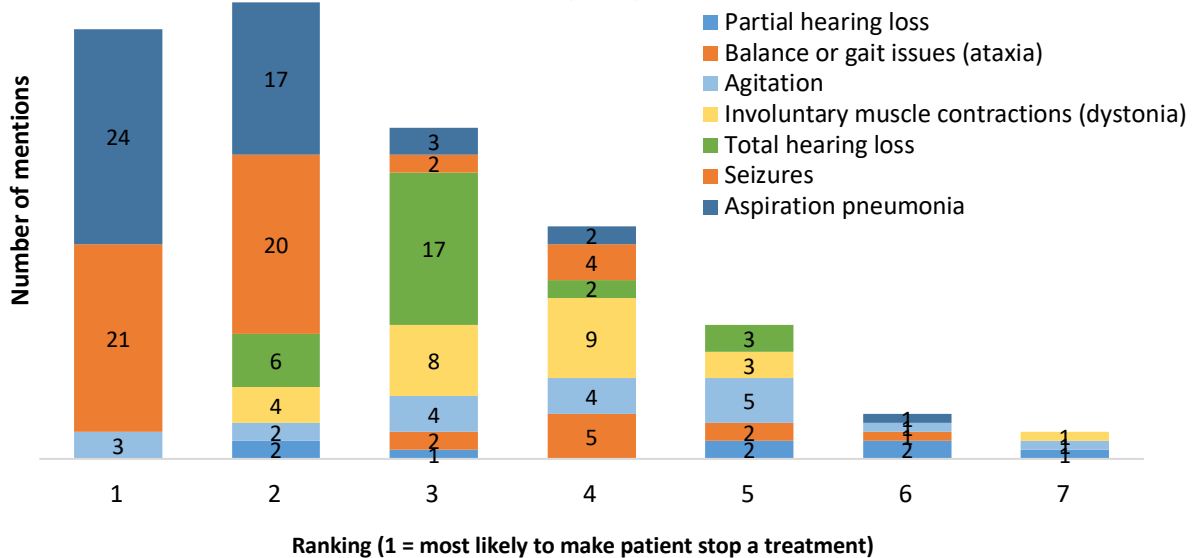


Fig. 16: Willingness to tolerate side effects of a treatment to significantly slow NPC progression (n=37)



Respondents were also asked whether certain side effects would make them stop taking a treatment. A large majority (around 80 percent) said the occurrence of aspiration pneumonia or seizures would make them stop taking a treatment. Over half of respondents (61 percent) said they would stop a treatment if a caused total hearing loss, although the data shown in Figures 14-16 suggests that they would be more likely to continue the treatment if the hearing loss could be corrected promptly with a hearing aid. Recognizing that a hypothetical treatment could cause multiple side effects, respondents were also asked to rank the side effects that would make them stop taking a treatment (see Figure 17 below). Most respondents ranked aspiration pneumonia and seizures as the first or second reason they would stop a treatment.

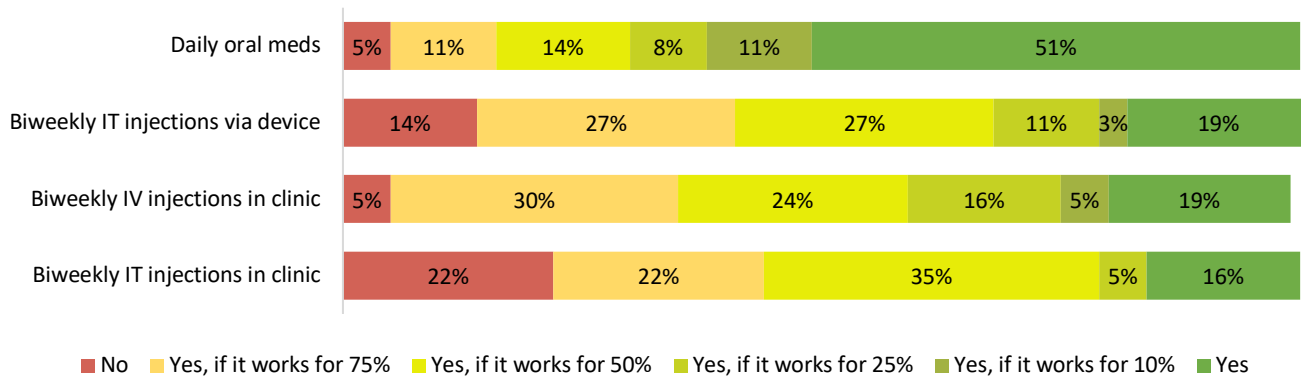
Fig. 17: Rankings of side effects that would make patients stop taking a treatment (n=38)



PREFERENCES FOR TREATMENT ACCESS AND ROUTE OF ADMINISTRATION

Beyond offering a way to learn more about NPC patients and caregivers’ views on the benefits of treatments and possible adverse effects, the survey also included questions about respondents’ views on how and where treatments could be offered. As shown in Figure 18, a large majority of respondents are willing to take treatments through a variety of routes of administration even if there is a high degree of uncertainty about whether the treatment will work. Not surprisingly, the largest percentage (51 percent) of respondents were willing to take oral medications, the least invasive treatment option, even if they have no assurance that it might work.

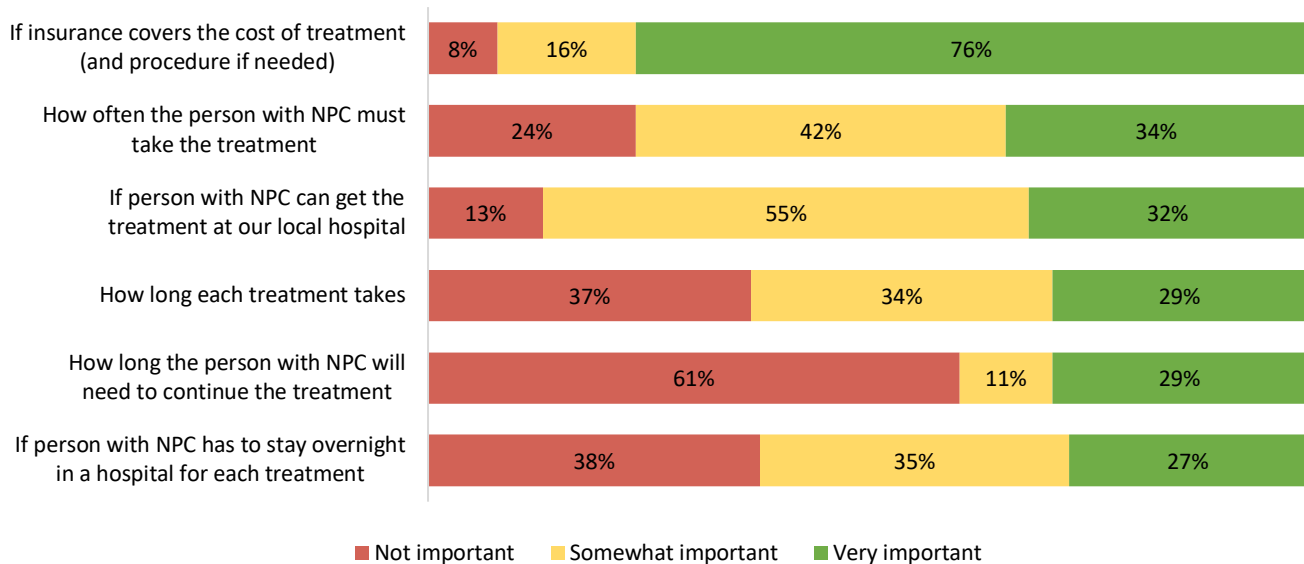
Fig. 18: Willingness to try different routes of treatment administration (n=38)



There were minimal differences between respondents’ willingness to have biweekly IT injections in a clinic or via a device that is worn at all times, perhaps indicating either that wearing a device would be seen as burdensome or that biweekly trips to a clinic are not seen as a significant burden. The latter is supported by respondents’ answers to a question about how far they would be willing to travel to a doctor’s office for a biweekly treatment. Half would be willing to travel up to two hours each way by plane and one quarter would be willing to travel up to four hours by car. The remaining quarter of respondents said they would only be willing to travel up to one hour by car. Right now, many NPC families already travel long distances to get treatments, so this data is not surprising. It does highlight, however, the high level of unmet medical need and the small number of clinicians and hospitals that have the expertise and capacity to treat people with NPC.

Although people with NPC and their caregivers may be willing to travel long distances to get treatment on a regular basis, these factors are still important to them when thinking about their willingness to try a potential new treatment. As shown in Figure 19, 88 percent of respondents feel that their ability to get a treatment at their local hospital is either very important or moderately important. Whether they have to stay overnight at a hospital, however, is less important. A majority of respondents also rate the frequency and duration of each course of treatment as at least moderately important, but most do not seem to have concerns about how long they might have to remain on a treatment. For a progressive, fatal condition like NPC, the prospect of having to be on a treatment for life—even one that requires frequent trips to a doctor’s office or hospital a good distance from their home—appears to be preferable than the alternative of having no effective treatment.

Fig. 19: Importance of access-related factors (n=38)



Despite respondents’ willingness to try treatments with fairly burdensome routes of administration and geographic access challenges, they remain concerned about the potential cost of future treatments. Over 90 percent of all respondents rated insurance coverage of treatment as at least moderately important and 76 percent rated it as very important. As is the case for other rare disease communities, developing an effective treatment is only half the battle: a truly successful treatment must also be accessible by those who need it.

PREFERENCES FOR POST-APPROVAL MONITORING

Given that any future treatment approved for NPC may be required to have post-approval monitoring, the survey included one question about the types of monitoring in which respondents would be willing to participate. A large majority (89 percent or more) were willing to participate in any of the types of monitoring listed. See details in Table 2 below.

Table 2: Percentage of respondents willing to participate in various post-approval monitoring approaches for a newly approved treatment for NPC (n=38)

Monitoring Approach	Percent
Yearly cognitive and/or motor skills testing in the doctor’s office	100%
Neurological assessments every six months in the doctor’s office	97%
Daily use of a “smart watch” or other wearable monitoring device	97%
Monthly visits to the doctor’s office	95%
Yearly swallow studies in the doctor’s office	89%
Monthly phone surveys	89%
Monthly online surveys	89%

As with other hypothetical treatment burdens, NPC patients and their caregivers have a high tolerance for adhering to post-approval monitoring requirements if it means they can get access to an approved treatment.

CONCLUSION

NPC is a devastating disease that robs patients of their ability to live normal lives and, eventually, leads to their death. The unmet medical need for this population is extremely high and patients and their caregivers have a high tolerance for the side effects and treatment access burdens that might be associated with a future treatment. They would most value a treatment that can preserve one of the most basic human needs—the ability to eat and drink—as well as treatments that can maintain the patient’s ability to understand and engage with the world around them (cognition). Although survey respondents might stop a treatment that causes serious side effects like aspiration pneumonia or seizures, they have a fairly high tolerance for other side effects, even if those effects are long term. As demonstrated by the global participation in this survey and the high level of engagement from the NPC community on past PFDD activities, NPC patients and caregivers stand ready to do what they can to advance treatments and, eventually, cures for this disease.

APPENDIX 1: SURVEY QUESTIONS

Patient & Caregiver Perspectives Survey for Benefit-Risk Calibration of Potential NPC Treatments

*indicates a required question

Introduction and Consent

This survey is designed to collect information about your priorities and preferences for treating Niemann-Pick Type C. It is organized by the NPC Therapy Accelerator Initiative. In the survey, you will read about hypothetical treatments for Niemann-Pick Type C. Some parts of the potential treatments described in this survey are based on real and investigational treatments and some are hypothetical. The information collected here is important to help the U.S. Food and Drug Administration (FDA) understand your thoughts and feelings about potential treatments for NPC.

This survey is intended for parents and current and past caregivers of those with Niemann-Pick Type C. Those who have multiple children with Niemann-Pick Type C should **complete one** survey for each child, and only one survey should be submitted for each child (e.g., two parents should not complete the survey separately on behalf of the same child). 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.

Your participation in this survey is optional and if you start the survey, you can stop at any time. The survey takes about 30 minutes. 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]*
 - a. I consent
 - b. I do not consent

Part I: Contact and Background Questions

2. ***Your first and last name:** _____
3. ***Your phone number and/or email address**
 - a. Phone number: _____
 - b. Email address: _____
4. ***Do you live in the United States?**
 - a. Yes
 - b. No
5. ****(If they answer Yes to previous question)*** Please enter your ZIP/postal code. _____
6. ****(If they answer No to question #4)*** Please enter the country where you live _____
7. ***Which is true about you? I am the _____ of the person with NPC.**
 - a. Biological father
 - b. Biological mother
 - c. Adoptive father
 - d. Adoptive mother
 - e. Grandmother who is a guardian
 - f. Grandfather who is a guardian
 - g. Spouse
 - h. Friend or caretaker with no direct relation
 - i. Other. Please describe: _____
8. ***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?**
 - a. Current caregiver
 - b. Former caregiver
9. ***(For people who selected b for Q8)*** *Date the person with Niemann-Pick Type C passed away. _____

Part II: Demographic Information

10. *Date of birth of person with Niemann-Pick Type C disease. _____

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

- a. Male
- b. Female
- c. Other
- d. Do not wish to disclose

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

- a. Hispanic/Latino
- b. Non-Hispanic/Latino
- c. Do not wish to disclose

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

- a. American Indian or Alaska Native
- b. Asian
- c. Black or African American
- d. Native Hawaiian or Other Pacific Islander
- e. White
- f. Other
- g. Do not wish to disclose

Part III: Current Disease State and Symptoms

[Introductory page]

For the questions in this section, please consider that every child is unique and may not match the descriptions perfectly. Please select the answer that is the best fit.

- 14. Niemann-Pick Type C is categorized by different ages of onset. These ages of onset refer to major neurological 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 the age of onset for the person with NPC.**
- Early infantile form / Visceral-neurodegenerative (typical onset at <2 years old)
 - Late infantile form / Neurodegenerative (typical onset between 2 and 6 years old)
 - Juvenile form / Neurodegenerative (typical onset between 6 and 15 years old)
 - Adult form / Psychiatric-neurodegenerative (typical onset at >15 years)
- 15. Choose the option that best describes the current walking or ambulation abilities of the person with Nieman Pick Type C. The person with Niemann-Pick Type C usually:**
- Walks independently
 - Walks independently with occasional clumsiness
 - Walks independently but with an ataxic (unsteady and/or staggering) gait
 - Walks but needs a cane, walker, or other gait supporter
 - Uses a wheelchair
 - Is confined to bed
- 16. Choose the option that best describes the current swallowing abilities of the person with Nieman Pick Type C. The person with Niemann-Pick Type C usually:**
- Can swallow liquids and solids with no difficulty
 - Sometimes has trouble swallowing (i.e., occasional, not at every meal in a given day)
 - Consistently has trouble swallowing (i.e., frequently, at almost every meal in a given day)
 - Can eat or drink on their own but sometimes uses a feeding or gastrostomy tube for additional nutrition.
 - Is unable to safely eat or drink; requires use of a feeding or gastrostomy tube
- 17. Choose the option that best describes the current fine motor skills of the person with Nieman Pick Type C. The person with Niemann-Pick Type C usually:**
- Has fine motor skills considered normal for their age
 - Can grasp and move small objects with only occasional difficulty
 - May need a few tries to grasp or move small objects
 - Consistently has trouble grasping or moving small objects, needs help with daily activities like using a spoon or brushing their hair
 - Has very limited fine motor skills
- 18. Choose the option that best describes the current cognitive skills of the person with Nieman Pick Type C. The person with Niemann-Pick Type C usually:**
- Has cognition considered normal for their age
 - Has mild delays but most cognitive skills are considered normal for their age
 - Has some delays and requires additional assistance such as a modified school curriculum

- d. Is losing their cognitive skills
- e. Shows minimal cognitive function

19. Choose the option that best describes the current speaking abilities of the person with Nieman Pick Type

C. The person with Niemann-Pick Type C usually:

- a. Is a baby under 18 months who is too young to speak
- b. Speaks normally for their age
- c. Mostly speaks normally but slurs some words
- d. Frequently slurs words and is difficult to understand
- e. Is unable to express himself or herself verbally but communicates using sounds and/or gestures
- f. Has almost no ability to communicate

20. Over the last year, have the following symptoms of the person’s Niemann-Pick Type C gotten better, stayed the same, or gotten worse? What about over the last five years?

Choices for each

- **Gotten better**
- **Stayed the same**
- **Gotten worse**
- **For last five years, also include “N/A – child less than five years old”**

	Last Year	Last Five Years
Ambulation / walking Issues		
Cognitive impairment		
Difficulty swallowing		
Fine motor skills issues		
Speech problems		

21. Over the last year, have the person with Nieman Pick Type C’s ability to do the following activities gotten better, stayed the same, or gotten worse? What about over the last five years?

Choices for each

- **Gotten better**
- **Stayed the same**
- **Gotten worse**
- **For last five years, also include “N/A – child less than five years old”**

	Last Year	Last Five Years
Eating or drinking		
Participation in sports or physical activities		
Personal care (dressing, bathing, toileting)		
School or work		
Social activities		

Part IV: Treatments

22. Is the person with Niemann-Pick Type C currently taking any of the following medications or experimental drugs? Have they taken any of these medications or experimental drugs in the last year?

	Currently Using	Used in Last Year
Allopregnanolone		
Anti-cataplexy medications		
Antidepressants		
Antipsychotics for psychosis		
Antiseizure medications		
Arimoclomol		
Botox		
Cyclodextrin (intravenous administration)		
Cyclodextrin (intrathecal administration)		
Miglustat (Zavesca)		
N-Acetyl-L-Leucine (IB1001)		
Sleep aids		
Vorinostat		

Part V: Treatment Preferences

23. When thinking about the effects of a potential treatment, which of the following activities of daily living would you find most important for the person with Niemann-Pick Type C to maintain or restore?

- a. Eating/drinking
- b. Exercise or participation in sports/physical activities
- c. Personal care such as dressing, bathing, using the toilet
- d. School or work performance
- e. Social activities

24. Imagine a hypothetical treatment for Niemann-Pick Type C that can offer only one benefit while all other symptoms would continue to progress (get worse). Which treatment would you choose?

- a. A treatment that would improve or maintain ambulation/walking abilities
- b. A treatment that would improve or maintain cognition
- c. A treatment that would improve or maintain swallowing abilities
- d. A treatment that would improve or maintain fine motor skills
- e. A treatment that would improve or maintain speech abilities
- f. A treatment that would improve psychological behavior

25. Now imagine that the treatment you chose will only work for a certain percentage of people. Would you still be willing to have the person with Niemann-Pick Type C take the hypothetical treatment? (Y/N choices for each)

- a. Works for 75-100% of people
- b. Works for 50-74% of people
- c. Works for 25-49% of people
- d. Works for 10-24% of people
- e. Works for less than 10% of people

Part VI: Tolerance for Side Effects

[Introductory page]

Imagine three hypothetical treatments for Niemann-Pick Type C that will slow the progression of all symptoms of the disease. Each of the treatments will slow disease progression to a different extent:

- 1) Treatment 1 will **slightly** slow the progression of Niemann-Pick Type C: by up to one year compared to no treatment.
- 2) Treatment 2 will **moderately** slow the progression of Niemann-Pick Type C: by 3-5 years compared to no treatment.
- 3) Treatment 3 will **significantly** slow the progression of Niemann-Pick Type C: by 8-10 years compared to no treatment.

All of these treatments have the potential to cause short- or long-term side effects. In the next three questions, you will be asked whether you would be willing to have the person with Niemann-Pick Type C take each of these three treatments if it resulted in certain side effects.

26. The person with Niemann-Pick Type C has the option of taking the hypothetical Treatment 1 which will **slightly slow the progression of all symptoms of the disease (by up to one year compared to no treatment). Treatment 1 may result in one or more of the side effects listed below. Please use the drop-down menus to indicate whether you would be willing to have the person with Niemann-Pick Type C take Treatment 1 if it caused that side effect.**

Drop-down options for each AE:

- ***Yes, including if side effects are long-term***
- ***Yes, but only if side effects last less than one week***
- ***No, would not choose Treatment 1 with this side effect***

- a. Back pain
- b. Balance or gait issues (ataxia)
- c. Diarrhea
- d. Fatigue
- e. Fevers
- f. Hearing loss
- g. Hearing loss that is correctable with a hearing aid
- h. Vomiting

27. The person with Niemann-Pick Type C has the option to take the hypothetical Treatment 2 which will **moderately slow the progression of all symptoms of the disease (by 3-5 years compared to no treatment). Treatment 2 may result in one or more of the side effects listed below. Please use the drop-down menus to indicate whether you would be willing to have the person with Niemann-Pick Type C take Treatment 2 if it caused that side effect.**

Drop-down options for each AE:

- ***Yes, including if side effects are long-term***
- ***Yes, but only if side effects last less than one week***
- ***No, would not choose Treatment 1 with this side effect***

- a. Back pain
- b. Balance or gait issues (ataxia)
- c. Diarrhea
- d. Fatigue
- e. Fevers
- f. Hearing loss
- g. Hearing loss that is correctable with a hearing aid
- h. Vomiting

28. The person with Niemann-Pick Type C has the option of taking the hypothetical Treatment 3 which will significantly slow the progression of all symptoms of the disease (by up to one year compared to no treatment). Treatment 3 may result in one or more of the side effects listed below. Please use the drop-down menus to indicate whether you would be willing to have the person with Niemann-Pick Type C take Treatment 3 if it caused that side effect.

Drop-down options for each AE:

- ***Yes, including if side effects are long-term***
- ***Yes, but only if side effects last less than one week***
- ***No, would not choose Treatment 3 with this side effect***

- a. Back pain
- b. Balance or gait issues (ataxia)
- c. Diarrhea
- d. Fatigue
- e. Fevers
- f. Hearing loss
- g. Hearing loss that is correctable with a hearing aid
- h. Vomiting

29. Select any side effects that would make you decide to have the person with Niemann-Pick Type C stop taking a treatment for the disease. You may select any number.

- a. Agitation
- b. Aspiration pneumonia
- c. Balance or gait issues (ataxia)
- d. Involuntary muscle contractions (dystonia)
- e. Partial hearing loss
- f. Total hearing loss
- g. Seizures

30. Please rank those side effects that would make you decide to have the person with Niemann-Pick Type C stop taking a treatment for Niemann-Pick Type C from mostly likely to least likely. You can create the rankings using the drop-down arrows or by clicking and dragging the choices into the order you want.

- a. *Options are based on selections made in previous question*

Part VIII: Preferences for Treatment Administration and Access

31. Imagine a hypothetical treatment for Niemann-Pick Type C that will **slightly slow the progression of all symptoms. Patients can take this treatment in multiple ways. Please choose all of the ways in which you would be willing to have the person with Niemann-Pick Type C take this treatment.**

Dropdown menu choices for each:

- Yes, but only if it works for at least 75% of people
 - Yes, but only if it works for at least 50% of people
 - Yes, but only if it works for at least 25% of people
 - Yes, but only if it works for at least 10% of people
 - Yes, without any assurance it will work
 - No, not willing to choose a treatment taken this way
- a. Intrathecal (spinal) injections performed in a clinic every two weeks
 - b. Intravenous (vein) injections performed in a clinic every two weeks
 - c. Intrathecal (spinal) injections performed every two weeks via a device that is worn full-time
 - d. Daily pills taken by mouth

32. Consider the following access-related factors of a potential new treatment for Niemann-Pick Type C. For each factor, indicate how important it is to you. (Choices: *Very important, somewhat important, not important*)

- a. If insurance covers the cost of treatment (and procedure if needed)
- b. If the person with Niemann-Pick Type C can get the treatment at our local hospital
- c. If the person with Niemann-Pick Type C has to stay overnight in a hospital for each treatment
- d. How often the person with Niemann-Pick Type C must take the treatment
- e. How long each treatment takes
- f. How long the person with Niemann-Pick Type C will need to continue the treatment

33. Imagine a hypothetical treatment for Niemann-Pick Type C that must be given in a doctor's office every two weeks. How far would you be willing to have the person with Niemann-Pick Type C travel to get these treatments?

Note: for options involving flights, please assume that the current COVID-19 infection risks are not a concern.

- a. No more than one hour each way by car
- b. Up to four hours each way by car
- c. Up to two hours each way by plane

Part IX: Preferences for Post-Market Surveillance

34. When a new treatment is approved, the FDA or other regulatory agency sometimes requires patients taking the treatment be monitored to collect more data on the treatment. If the person with Niemann-Pick Type C was taking a new treatment for the disease, which of the following would you be willing to have them do or do on their behalf? Select all that apply.

- a. Monthly visits to the doctor's office
- b. Neurological assessments every six months in the doctor's office
- c. Yearly swallow studies in the doctor's office
- d. Yearly cognitive and/or motor skills testing in the doctor's office
- e. Monthly phone surveys
- f. Monthly online surveys
- g. Daily use of a "smart watch" or other wearable monitoring device

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 therapy development for Niemann-Pick Type C disease. Any data collected here will only be shared in a summarized, anonymous manner.