Duke | MARGOLIS CENTER for Health Policy

Endpoint Considerations to Facilitate Drug Development for Niemann-Pick Type C (NPC)

Virtual Public Workshop

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Workshop Summary

Executive Summary

Niemann-Pick type C (NPC) is a lethal neurodegenerative lysosomal disease caused by pathogenic variants in either the *NPC1* or *NPC2* gene. Individuals with NPC have significant unmet treatment needs as there are no therapies currently approved in the United States for the treatment of NPC. In order to advance drug development, stakeholders must work together to identify strategies to overcome challenges associated with drug development for rare diseases and better support efficient and effective NPC clinical trials.

The Robert J. Margolis, MD, Center for Health Policy at Duke University and the U.S. Food and Drug Administration (FDA) convened a group of experts to discuss clinical endpoints relevant to clinical trials and innovative measurement strategies with the overall goal of supporting the development of safe and effective treatments for those living with NPC. During this workshop, it was emphasized that researchers face significant challenges in measuring a disease that, from their perspective, can appear exceptionally slow and uneven in progression. However, it was also expressed by stakeholders throughout the workshop that to patients and their families, progression is fast-moving and pervasive as an NPC diagnosis has far-reaching ramifications on the lives of those impacted by the disease.

Despite the existing challenges, research for potential therapies and methodologies to assess NPC therapies is advancing. Families continue to share what they identify as successes with NPC interventions and describe improvements that are meaningful to them. It is critical that all stakeholders are using the right measures to assess NPC therapeutics. Measures must be sensitive enough to capture scientifically what patients and families are experiencing and sharing anecdotally. Further objective measures could add to the evidence for clinically meaningful benefits for NPC therapies.

Workshop participants discussed a number of potential strategies for making the NPC drug development process more efficient, including mechanisms of feedback between regulatory agencies, more ongoing collaboration among all stakeholders, and learning from some of the product submissions that have not been successful in achieving FDA approval. Participants highlighted the importance of data sharing, aggregating available data, and building on the existing database of patient natural history. Of note, many participants stressed that the existing natural history data are invaluable and not replicable as the treatment paradigm has progressed to a time where most patients may be using at least one investigational or off-label product. Throughout the workshop, participants also discussed the importance of having access to care and treatment close to patients' homes and how telemedicine and other methods of decentralization could greatly improve access to clinical trials.

The consensus shared throughout this workshop is that building upon and enhancing existing measures, applying methods and analytics used for assessing treatments in other rare and heterogenous diseases,

and continuing to engage all stakeholders – especially patients and caregivers – are essential to facilitating successful drug development for NPC.

Workshop Disclaimer

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Introduction and Clinical Overview of NPC

NPC is a devastating and serious disease that tremendously impacts both children and adults. As a highly heterogeneous disease, clinical assessments may not consistently or adequately reflect disease presentation, progression, or clinically meaningful improvements from potential therapeutics in all patients with NPC. For product approval, data must demonstrate that the benefits of a product outweigh the risks.[1] However, the FDA has a long-standing commitment to regulatory flexibility for serious and life-threatening rare conditions with an unmet treatment need. This regulatory flexibility is applicable to diseases like NPC. The FDA works with drug developers to select scientifically valid and optimal endpoints that meet regulatory standards for their specific development programs.

Clinical Overview of NPC

NPC is an autosomal recessive lethal neurodegenerative lysosomal disease caused by pathogenic variants in either the *NPC1* or *NPC2* genes. These genes are responsible for intracellular lipid transport. Mutations result in impaired intracellular transport of cholesterol and other lipids, leading to accumulation of lipids and unesterified cholesterol in multiple organs including the liver, spleen, lungs, and brain.[2] In neurons, the result of this accumulation is neuronal death. Additionally, cellular stress occurs due to decreased cholesterol bioavailability. Neuroinflammation, including microgliosis and astrogliosis, can lead to progressive neurological impairment, in particular cerebellar ataxia, and deficiencies in fine motor function, speech, and swallowing. Vertical supranuclear gaze palsy (VSGP) is also seen in patients with NPC, and a major component of the disorder is cognitive impairment and dementia.

The estimated incidence of NPC is one case per 100,000 live births.[3] Although disease presentation can vary widely, most patients diagnosed with NPC typically experience progressive neurological symptoms and organ dysfunction. NPC most-commonly presents during childhood, but an increasing number of patients with adult-onset symptoms are being identified. The average age of death of patients with childhood-onset NPC is 13 years old. The rarity of NPC, the wide range of onset age and symptom presentation, and the complexity of diagnostic testing has led to common misdiagnosis or delayed diagnosis and can make proper care more difficult for patients to access.

There are currently no therapies approved in the United States for the treatment of NPC. Miglustat, an iminosugar approved for Gaucher's Disease in the United States and for NPC in several other countries, is considered a standard of care by some clinicians and patients with NPC and is commonly prescribed off-label for the treatment of NPC. The cost of miglustat, especially given its off-label use in the United States, can be prohibitive for patients with NPC.

Drug Development Challenges

Clinical trials for any rare disease can be challenging due to small population size and a limited ability to fully characterize both clinical and laboratory-based aspects of disease progression. The extremely low incidence of NPC makes powering clinical trials for NPC particularly challenging. Clinical trials may take longer to complete due to limited enrollments, and trials for NPC treatments may need to engage patients from around the globe to ensure an adequate number of trial subjects. Disease pathophysiology and clinical symptoms both guide and inform outcome measures and therapeutic trial designs. As NPC is a highly heterogeneous disease, some assessments of symptoms and impacts selected as an endpoint for a clinical trial may not reflect disease presentation, progression, or clinically meaningful improvements for all patients with NPC.

Workshop Objectives and Scope

The Duke-Margolis Center for Health Policy, under a cooperative agreement with the FDA, hosted a workshop to support advancements in the selection and development of endpoints for NPC clinical trials. The overall goal of the workshop was to support drug development for NPC by advancing the conversation around successful NPC clinical trial endpoint development and selection. This workshop was meant to balance the conversation between immediate needs and long-term goals of NPC product development. Workshop participants reviewed endpoint considerations in NPC and discussed challenges and opportunities to support product development, functional assessments that could serve as clinical endpoints in NPC clinical trials, and innovative strategies to support product development, such as digital technology and biomarkers.

While the workshop on endpoint considerations was focused on scientific discussions, patients are the primary stakeholder in medical product development, and therefore, patient and caregiver perspectives were incorporated throughout the workshop to maintain the focus on what is meaningful and feasible for individuals directly impacted by NPC. Of note, experts in neurodegenerative diseases, small trial design and/or endpoint development from outside the NPC field were also included throughout this workshop to lend insights from other relevant fields in order to supplement, but not to supplant, the existing knowledge and evidence shared by NPC experts. Participants in this workshop discussed endpoints for NPC clinical trials, but not specific drugs or the use of expanded access as these were beyond the scope of this workshop. Broader conversations will be needed to address the full range of challenges and opportunities for NPC drug development.

Session 1 - Challenges and Opportunities with the NPC Clinical Severity Scale (NPCCSS)

Patient and Caregiver Perspective

During this session, a caregiver shared his experience with his two children diagnosed with NPC, whose disease progression differed dramatically from one another. One child diagnosed at age eight experienced rapid decline, was in a wheelchair by age 11, and had passed away by her late teens. Reflecting on his family's experience with the initial diagnosis, the caregiver stressed that "when someone tells you [that] you have five years left with your child, that's really not a slowly progressing disease." The caregiver shared that his other child with NPC is currently experiencing a level of independence, although the disease is still progressive. Now in his early twenties, the other child is able to work part-time. The caregiver emphasized that NPC is always fatal, sharing that "we know that NPC is still stealing neurons every day, just more slowly with the interventions."

The NPC Clinical Severity Score (NPCCSS) comprises 17 domains with the intent to capture and quantify the full range of disease presentation and severity across a wide range of ages.[4] NPC has very broad phenotypic heterogeneity in terms of age of neurological disease onset and specific symptom complex. While progression may vary from patient to patient, and symptom severity can vary from day to day, over the long term the disease is invariably progressive. However, each individual patient may progress in different domains at different rates, and there is no single domain that alone can be applied to every patient. To address this challenge, the NPC-specific domains were based on neurological

impairments that allow for a calculation of a composite score to indicate disease severity and assess progression over time. An abbreviated five-domain NPCCSS (5DNPCCSS), a clinician-reported outcome (ClinRO) assessment, was created for greater clinical utility and to support research by using the five functional areas selected as the most clinically meaningful to patients, caregivers, and NPC clinical experts when assessing disease progression.[5] These five domains are ambulation, fine motor skills, swallowing, cognition, and speech.[6]

While the 5DNPCCSS has been a valuable resource for understanding disease progression, there have been some challenges with interpreting results, especially for shorter duration clinical trials. One participant expressed that gaps in validity evidence in the 5DNPCCSS could potentially be addressed with future research. For example, more evidence may be needed to ensure that response options in each domain are relevant for the full age spectrum being studied, that the different score options within a single domain do not overlap, and that the response options are clearly defined and consistently interpreted by clinical experts. Qualitative analyses, such as cognitive interviewing (also called cognitive debriefing) with clinical experts in each of the five functional areas, could be conducted to address this gap in validity evidence. In addition, it is important to confirm that the clinical outcome assessments are measuring what they are intended to measure when compared to other well-defined and reliable assessments. Validity evidence could also be generated from quantitative analysis of existing data for each of the domains through comparison to other standardized assessments of similar concepts. Finally, there is a need to ensure that the 5DNPCCSS has standardized implementation – that the same assessment happens the same way with every patient, by every clinician, at every site. Strategies for standardizing implementation could include harmonized training materials and standardization of assessment.

Some participants shared recently published research that evaluated the quantitative validity of some of the domains of the 5DNPCCSS. For example, the clinician-scored ambulation domain correlates highly with the Neurocom Sensory Organization Test, a computerized balance assessment. The clinician-scored Fine Motor Abilities Rating correlated with the 9-hole and Purdue pegboard tests. The Speech domain correlated with the Clinical Evaluation of Language Fundamentals (CELF) formulated sentences test. Additionally, a specialized Intelligence Quotient-Development Quotient (IQ-DQ) test was created based on the Mullen Scales of Early Learning (MSEL) and Weschler Adult Intelligence Scale for the entire age range of NPC patients and has shown that the cognitive domain correlates with the full scale IQ, verbal IQ, and nonverbal IQ. A team of researchers who regularly assess patients on the 5DNPCCSS have created a raters' scoring guide and a set of training videos, each of which showed high inter-rater reliability when used. Training materials such as these could be incorporated more broadly and universally when implementing the 5DNPCCSS in clinical trials. Another strategy suggested by a participant would be to modify the 5DNPCCSS to incorporate a mid-range of scores into training materials to help guide clinicians. Standardized implementation could also include other supportive assessments, such as a caregiver daily diary to prospectively and systematically record observation.

It is essential to also recognize that some aspects of NPC that are clinically important may not be suitable for inclusion in a primary efficacy endpoint within the constraints of a clinical trial. Cognition is an important area of functioning identified by clinical experts, patients, and their families and is critical for long-term assessment of patients with NPC. However, existing evidence from the NPC natural history study indicates that the rate of decline in cognitive functioning does not align well with the relatively shorter-term clinical trials which are typically one year or less in duration.[7] Declines in cognitive function occur over many years, and thus existing assessments of cognitive function may not be able to detect change in a study population within the timeframe of a typical clinical trial for NPC.

There has been interest within the NPC research community in exploring novel trial designs and analytic methodologies to improve the clinical measurement process for this disease, including N-of-1 trials and use of the natural history data for comparators in place of a traditional placebo group. Some participants highlighted concerns that running a placebo-controlled trial for a progressive, fatal disease in a pediatric population may not be ethical. There has also been interest in further refining and enhancing the interpretation of measurements with the use of additional clinical data, and the use of other measures or biomarkers to enhance endpoint measurements. These new methodologies could bolster measures such as the NPCCSS, and further improve the efficiency of clinical trials considering the small population size, the heterogeneity of the population, and the irreversible effects of the disease.

Session 2: Functional Measures of Swallowing

Patient and Caregiver Perspective

A caregiver, who is a speech-language pathologist by training, shared her perspective as a parent of two sons living with adult-onset NPC. The initial presenting clinical symptoms of disease were psychiatric, which led to years of misdiagnosis. The caregiver's sons are currently participating in two different trials. During the opening statement, the caregiver stated of her adult children's access to investigational products that "my husband and I feel that both treatments have allowed them to maintain their separate levels of independence, and that their progression has not been what we were initially led to expect." Speaking on the need to include patient and caregiver observations as part of swallowing evaluation protocols, the caregiver shared that "as a clinician and a parent, I feel strongly one can never replace what is observed on a day to day basis."

Swallowing is one of the five domains in the abbreviated 5DNPCCSS, selected by patients, caregivers, and clinical experts for its impact on both patient safety and quality of life. Across the age spectrum, more than 80 percent of patients with NPC develop difficulties swallowing, or dysphagia, due to the impact of disease progression on sensory and motor coordination. For patients with NPC, the average age at which dysphagia occurs is 14 to 16 years old, but it can take 10 to 11 years from the onset of symptoms to reach dysphagia. The presence of dysphagia can pose significant risks for choking, aspiration, and pneumonia.

While swallowing has been identified as a key symptom of NPC, assessing dysphagia and its progression as well as using swallowing as a clinical trial endpoint can be difficult. Ideally, a swallowing study should be feasible for the full range of NPC patient ages from infants to adults. There have been difficulties in the interpretation of swallowing studies stemming from the heterogeneity of the disease and lack of standardization in assessment methodology across and within disciplines. In addition, medications taken for concomitant seizures, cognitive impairment, and behavioral health issues can all interplay with swallowing ability or the ability to measure longitudinal changes.

Swallowing is a complex neuromuscular process that develops throughout childhood, and there are a range of evaluations used to assess this process. Measures include patient, parent, or caregiver reports,

clinical severity scores, observational exams, and instrumental assessments such as Modified Barium Swallow (MBS)[1] or Fiberoptic Endoscopic Evaluation of Swallow (FEES).

The MBS assessment, also known as the Videofluoroscopic Swallowing Study (VFSS), consists of a patient swallowing a variety of food and liquids mixed with barium while being visually recorded via fluoroscopy. This evaluation is considered the standard for adults, but can be challenging for younger patients. In addition, this test exposes the patient to radiation, which carries risk, especially for younger children or when frequent testing may be required in the context of a clinical trial. While it can be useful for evaluating the pharyngeal phase, MBS evaluation of the oral phase of swallowing can be impacted by patient compliance with the testing methodology, particularly in the youngest patients. The VFSS requires special training to administer and interpret.

Another option for swallow evaluation is FEES, which involves inserting an endoscope through the nose and into the pharynx. This process can be difficult for many patients. Not all clinical sites are equipped to perform this assessment, so FEES may not be as useful for large-scale studies compared with other swallowing assessments. Of note, the oral phase of swallowing is not evaluated via FEES.

Participants highlighted some approaches that may help address the limitations of existing swallowing measures. Patient and caregiver diaries may help communication and longitudinal follow-up with speech-language pathologists to fill in gaps between swallowing assessments performed during clinical visits. Additionally, newer technologies, such as audiovisual diaries, may make swallowing evaluation more consistent by allowing videos taken in multiple distinct locations to be evaluated in one location by one – or even a small number of – evaluators.

While swallowing studies are valuable, there are associated burdens with each study that can make participation difficult for some patients and may make the measure less reflective of the patient's daily swallowing capabilities. For example, a patient may struggle with certain textures of foods at home that are not used in these assessments. To address this challenge, it can be beneficial for evaluators to discuss with patients or caregivers what types of foods and what part of the swallowing process they struggle with in advance of performing assessments. Additionally, taste and texture of the foods used in swallowing evaluations are often difficult for patients to tolerate, especially pediatric patients. While standardization of food type and texture is essential to generate consistent data, the selection of which foods to use in swallowing evaluations may introduce unintended biases as some patients may be more or less tolerant of the selected test substance.

Additional burdens include the significant distances patients can be required to travel in order to participate in trials at the specialized clinical sites equipped to carry out swallowing studies. This may decrease the patient population able to participate in trials or introduce bias. In addition, swallow studies can require active participation from patients, which can be difficult for some, especially pediatric patients or those experiencing cognitive challenges. While these challenges remain, the field of speech-language pathology is overall becoming more standardized, which may lead to additional opportunities for improving accessibility and standardization of swallowing measures in the future.

[1] *May also be referred to as the Modified Barium Swallow Study (MBSS).*

Session 3: Functional Measures of Ambulation, Speech, and Fine Motor

Patient and Caregiver Perspective

A caregiver shared her experience of her child's diagnosis with NPC at 18 months of age. Speaking about the initial lack of access to clinical trials, she shared that "we quickly began flying from LA to Chicago every other week to start an experimental medicine through expanded access." The caregiver shared that her child has been making steady progress since the start of this intervention five years ago; she has seen her child's cognition and mobility improve significantly. The caregiver emphasized that early intervention matters – while reversing the effects of NPC may not be a realistic goal, slowing progression is realistic. Speaking on measuring the success of different interventions, the caregiver further stated that "when these numbers show a slowing, or stalling of disease progression for that patient, it's very important that these numbers and endpoints be interpreted as a massive success – and it needs to be recognized as such."

As previously noted, all five domains of the 5DNPCCSS were selected based on what patients, their caregivers, and NPC clinical experts identified as most clinically important to patients with NPC. Ambulation, speech, and fine motor skills are three of the five domains, and are relevant to measuring disease state and progression in patients with NPC. The onset of NPC symptoms most commonly occurs during middle to late childhood. For these individuals, neurological abnormalities like cerebellar ataxia – or lack of muscle coordination – may be the first apparent symptoms of NPC. Children with cerebellar ataxia often have difficulties with balance and trouble with walking. Children with NPC may also experience progressive difficulty speaking and may lose previously acquired speech skills. Finally, fine motor skills are significant for the impact hand tremors or difficulty coordinating hand movements have on patients' everyday activities like eating, writing, and caring for themselves.[2]

While these symptoms are important for understanding the current disease state and progression of NPC, ambulation, speech, and fine motor skills can be difficult to assess for patients across the age spectrum. For example, very young children (0-2 years) would not be expected to have reached certain developmental milestones that may be relevant to the selected assessments. However, selection of alternative age-appropriate measurements to more accurately capture disease state in this age group can add further difficulties related to standardization across the patient population being evaluated.[2]

The selection of clinical outcome assessments for ambulation, speech, and fine motor skills must be informed by a thorough and well-characterized understanding of the disease and how it varies across patients, age groups, and phenotypes. Clinical evaluation tools have different strengths and weaknesses that must be considered, including that they may be appropriate for only certain age ranges. Additionally, assessments used to understand NPC disease state and progression should capture change that is meaningful, as understood by patients, caregivers, and clinicians. While performance on standardized tests can be helpful for purposes of clinical trials, it is also important to remember that standardized measures may not always accurately reflect how a patient functions in the real world. Assessment tools should be considered for reliability and relevance to outcomes that are important to patients, caregivers, and clinicians.

In general, there are several important measurement needs in NPC, including developmentally age-appropriate assessments for all domains using a multi-domain definition of function. Patients may

progress in ways that cannot be easily measured, including if they reach the floor or ceiling of a given scale. This can present challenges for a small, age- and ability-diverse population, who will demonstrate a wide range of abilities that must be measurable on a single scale. For example, the Peabody Developmental Motor Scale has been useful in assessing motor abilities of patients from birth to five years old. One caregiver stated, however, that this exam requires the patient to be able to perform specific functional skills three times consecutively in order to be scored at the next level. The caregiver shared their concern that a patient who improves in other motor skills could be measured as static if they cannot complete this specific skill. The Mullen Scales of Early Learning have been helpful in assessing cognitive, motor, and perceptual abilities of patients from birth to 68 months, but the assessment can be heavily dependent on the patient's level of engagement with the administrator. Of note, a child may score differently depending on whether they are engaged or bored.

Measurement for ambulation requires a comprehensive gait assessment to capture gait deviations expected from ataxia, such as step size or increase in base of support. Fine motor assessments would benefit from the ability to specifically capture hand-eye coordination that can be linked to caregiver reported outcomes. It is also important to define how multi-system impairments may impact accurate assessments, for example, how cognitive issues can impact a patient's performance on a fine motor assessment, or how fine motor skills may impact cognitive measurements.

If assessments are not sufficiently sensitive, then stabilization or slow improvement of symptoms may be lost or not detected, even though these outcomes may be meaningful to patients and families. Other analysis frameworks may be beneficial, such as interactive measurements in which a patient is assessed on what they can do in their own environment. Measurements like these include the ability to perform daily tasks such as brushing their teeth, eating with a utensil, or standing up from the floor.

Incorporation of multiple assessments and multiple types of statistical analysis will be important elements for optimizing measurement. Using a combination of raw scores, age equivalents, and normative scores may increase the likelihood of scores reflecting change and provide additional context to convey the impact of observed changes. A therapy that stabilizes or slows the decline of certain domains may not be reflected as an improvement in normative scores but may be considered a positive finding. In the context of a valid and reliable assessment, some measurement problems may be addressed in the analyses rather than by changing the measurements such as use of sophisticated models around raw scores rather than pre-coded items. It is important to consider how modifications to the data collection for NPC clinical trials impact comparisons to existing natural history data. Ideally, any modifications to the data collection would incorporate factors that allow comparison to existing natural history data.

Session 4: Exploring Digital Health Technology to Measure Functional Endpoints

Patient and Caregiver Perspective

An adult living with NPC and his father each shared their experience during this session.

During opening remarks, the adult living with NPC highlighted his experience with receiving investigational therapy and expressed concerns about continued access to existing investigational products. Speaking on his experience with his current treatments, he stated "it all comes down to that I live a normal life. I graduated from college with an Associate Degree in Fire Science. I work over 30 hours a week and drive a car. I do chores around the house and play with my dog. I enjoy going out with my friends to eat, go to movies, concerts and playing sports. Life is good."

The caregiver shared his perspective as a parent of two children with NPC, one of whom passed away from the disease at the age of 20. The caregiver emphasized that "NPC is a cruel disease; it damages your body every single second of every single minute of every single hour of every single day." Of note, he conveyed that the flexibility in FDA's approach to NPC drug development has not been apparent to members of the NPC community. The caregiver stressed that while patients and families are sharing the successes and meaningful outcomes they see in their day-to-day lives with investigational interventions, they feel that information is not necessarily being adequately captured or considered. Digital health technologies may add to the arsenal of tools available to researchers in the future. However, the caregiver further emphasized the importance of leveraging the existing natural history data in the immediate term.

Digital health technologies offer additional opportunities to collect meaningful and more frequent data from patients in clinical trials, as well as record real-world data throughout their clinical care. These digital technologies can ease collection of data from some traditional assessments and strategies available to NPC researchers, but could also foster the use novel measurements that may better reflect outcomes that matter to patients. However, it remains critical that stakeholders preserve and continue to leverage the natural history and other data collected over the years.

Many neurological diseases, such as Parkinson's disease and Alzheimer's, rely on rating scales as a basis for clinical evaluation. Rating scales may be subjective, insensitive, and categorical, which can create challenges for accurately reflecting the patient's symptoms and disease state. Additionally, given that these scales rely on episodic measurements, they may miss important events or mischaracterize trends during the course of a progressive disease. These challenges with rating scales may lead to false negatives in clinical trials, in which an effective treatment is measured as ineffective. Without measurements that are more objective, sensitive, and continuous, it may be incredibly difficult to identify, develop, and demonstrate efficacy of treatments for neurological diseases, including NPC.

Digital health technologies have multiple potential applications in supporting clinical assessments of patients with NPC. These technologies can be used to measure an existing endpoint, such as ambulation, and offer an opportunity to carry out continuous monitoring of symptoms using technologies such as wearables like Fitbit or Apple Watch. Other opportunities include passive monitoring of symptoms, such as through radio wave technology that measures patient activity 24 hours a day, which may provide a

better understanding of a treatment's impact on how a patient feels or functions. Collection of measures through digital health technologies alongside traditional collection of measurements could assess both the traditional measurement and the digital health technology being used. Digital health technologies offer an opportunity to capture both sensor-measured and patient-recorded data in the home and from the patient's day-to-day experience.

In addition, digital health technologies offer unique opportunities to ease the burden of clinical trial participation on patients and families as well as facilitate more efficient trials. Travel, especially over long distances to clinical sites, can be physically and financially exhausting for patients and families. Telehealth can help expand patient access to clinical trials and NPC clinical expert care by requiring less travel. Telehealth facilitates assessment in the home setting where a patient is most comfortable, and this may allow researchers to better see the full range of a patient's abilities rather than only a snapshot in what can be a less than ideal clinical environment. Importantly, telehealth could improve trial efficiency by facilitating decentralized trials and allowing more patients, both nationally and internationally, to be evaluated through participating trial sites. Furthermore, approaches supported by telehealth such as videographic analysis could increase interrater reliability by having the rater be the same for different sites.

For other neurological conditions, there have been apps created that allow caregivers to record functional abilities on a daily basis, such as brushing teeth, getting up from the floor, and eating with utensils. There may be some value in pursuing these technologies for assessment of individuals with NPC. As an emerging area, it is important to ensure researchers and regulators understand exactly what information is being captured and what is not. Digital health technologies may be best used initially in a complementary role to traditional clinical data collection rather than as a replacement for clinical scales.

There are limitations of digital health technologies and their applications that must be taken into consideration. While there is variability in the phenotype of NPC, there may also be diversity in patient's lives that must be accounted for when deploying digital health technologies to capture data in the real world. A digital health measurement must be interpreted in the context of people's diverse lives. Concerns about cybersecurity and data access also apply to digital health tools. Additionally, use of these technologies requires patients to have broadband, wireless, and the ability to use the technology, which may pose barriers for some patients and families. Finally, missing data and uninterpretable data may reduce the utility of the data collected through digital health technologies. Digital health technologies may produce enormous amounts of data, and it can be difficult to determine how best to analyze and interpret the resulting data. Researchers must have a plan for addressing these issues should they arise.

Session 5: Future Biomarker Considerations in NPC

Biomarkers are molecular, histologic, radiographic, or physiologic characteristics that can be measured as indicators of biological processes, pathogenic processes, or response to an exposure or intervention. The development of biomarkers is especially important in rare diseases such as NPC, as small patient populations, widely variable clinical presentation, and slow rates of progression in some patients can make it challenging to establish clinical efficacy through use of more traditional clinical trial measures.

Biomarkers can be used in various ways, such as to assist with the diagnosis and monitoring of a condition, and potentially to assess disease progression.[8] Biomarker categories of relevance to NPC include diagnostic, prognostic, and pharmacodynamic or response biomarkers. As compared to other

existing methods of NPC diagnosis and disease monitoring, biomarker testing may be generally rapid, lower-cost, and less invasive.

In order to be used in regulatory submissions, biomarkers require analytical and clinical validation, and can be validated through broad scientific consensus, through the FDA biomarker qualification process or by an individual submission by a company to the FDA. Of note, a biomarker that has been validated to predict a specific clinical benefit could be accepted as a surrogate endpoint for future trials. Biomarker data could also be used as confirmatory evidence for effectiveness alongside other data, such as data from clincial assessments. Furthermore, drugs can be granted accelerated approval based upon a biomarker that has not been validated but is "reasonably likely" to predict clinical benefit, meaning that clinical benefit is supported by mechanistic or epidemiological data. Animal model data may be used to bolster clinical data in support of biomarker applications.

Several types of biomarkers have been researched for NPC, but most that have been well-characterized are produced in peripheral tissue and have limited use as a biomarker for central nervous system (CNS) response. Research has identified several cholesterol oxidation products (oxysterols) that are detectable before the onset of symptoms and associated with disease progression. Oxysterols have high specificity and can be used to rapidly diagnose NPC from a drop of blood, and may have additional potential as pharmacodynamic measures to monitor response to therapy.[6,9] Additionally, certain bile acids, primarily 3β,5α,6β-trihydroxycholanic acid and its glycine conjugate, can be used as diagnostic biomarkers and are being explored for potential as prognostic biomarkers.[10]

As NPC is fundamentally a disease impacting the CNS, there is some evidence that compounds generated in the CNS, including 24-hydroxycholesterol, could be useful as pharmacodynamic biomarkers for NPC.[8,11] There is also early research suggesting that biomarkers based on cerebral spinal fluid (CSF) proteins, such as CSF FABP3 and Calbindin D, could be useful as pharmacodynamic biomarkers.[12] More research would be needed before these biomarkers could be deployed in the clinicial studies for NPC therapies. Other biomarkers under investigation include acylphosphocholineserine (APCS), grey matter volumes and comparison subcortical volume,[13,14] and lysotracker staining.[15,16]

Despite advancements, there remain significant challenges with biomarker use in NPC. Generally, biomarkers do not represent the full outcome of a drug. Also, there may be a difference in when an intervention shows a change in a clinical outcome and when it shows a change in a biomarker. It is also difficult to statistically correlate changes in biomarkers to clinical improvement based on data from small patient populations. Large patient-to-patient variability in biomarker levels further make these hard to characterize and validate.

Because many of the biomarkers under investigation are relevant to other neurological diseases or lysosomal diseases, there may be opportunities for partnerships and collaboration among researchers in multiple disease spaces. Neurofilament light chain has been explored for many neurologic diseases and is a candidate biomarker for assessing neurodegeneration. It may be beneficial to aggregate data on biomarkers, or additionally to aggregate a bank of samples that could be tested for different biomarkers for different studies. A databank of healthy subjects' samples could be especially useful, providing a baseline or "normal" level for biomarkers that could be used as a comparator in trials for many different drugs.

Overall, there have been significant research advancements in the understanding and characterization of biomarkers for NPC, especially for diagnostic and prognostic biomarkers. Significant challenges

remain that will make it difficult to use biomarkers for NPC drug development in the near term, but research to move this area forward could provide major advances for NPC therapeutics in the future.

Session 6: Closing Panel and Forward Looking

Patient and Caregiver Perspective

Two caregivers spoke on their families' experiences with NPC during this session.

A caregiver shared the experience of his child, who when diagnosed with NPC at age six was only expected to live a few years. The caregiver shared that at the time of diagnosis the clinician "told us to go home and take pictures, enjoy the time you have." The caregiver's child, now 22, has been taking a product "off label" for 16 years and an additional investigational product for nine years and is still able to walk. The caregiver expressed that it is critical that patients and families have a voice in identifying meaningful clinical outcomes and in determining the risk tolerance for a given patient population. Additionally, he shared that researchers may be missing opportunities to collect data and patient experience through caregivers, nurses, doctors, and therapists who see and interact with the patient regularly. These individuals may be able to provide important insights into the patient experience as well as successes and setbacks in support of clinical trials.

A second caregiver participating in this session shared the experience of her child, who was diagnosed with adult-onset NPC at age 26 and has since passed away. The caregiver's child experienced mostly psychiatric symptoms initially, which made accurate diagnosis incredibly challenging; it took 12 years to get the diagnosis of NPC. The caregiver stressed that researchers and regulators cannot lose sight of the full spectrum of patients and families impacted by NPC and the differences in needs and priorities. The caregiver highlighted some of the unique challenges of adult-onset NPC, including the challenges of losing independence and additionally that "one of the most devastating parts of adolescent-adult onset is the emotional component. For young adults, it's knowing that your peers are moving forward in their lives, and you're moving backwards. For older adults, it's having a life and then knowing it's slipping away." Speaking on the rate of progression with adult-onset NPC, the caregiver shared that "regardless of age, when progression is happening to you or your loved one, it feels like every time you turn around, something else has been lost."

Reflecting on discussions from prior sessions, participants emphasized the importance of remembering that drug development programs in neurodegenerative diseases, including NPC, may not result in improvement in disease symptoms after treatment. Instead, the goal is to understand whether an intervention may result in stabilization or attenuation of the decline in the rate of disease progression. It is important that endpoint development and selection, as well as the measures used, for NPC clinical trials reflect this goal. Participants further stressed that the ultimate goal of NPC therapeutic development is not just to create small improvements in a subset of the population, but to identify multiple drugs that can impact the long-term course of disease across the NPC population.

The 5DNPCCSS has been a valuable tool and is used as a primary endpoint in NPC drug trials worldwide. Improvements and modifications to the 5DNPCCSS could reduce measurement error and subjectivity. However, participants stated that any modifications must be able to integrate with the existing data.

Among other applications, these data are essential to compare biomarkers and consider objective measurement scales for use in supporting NPC clinical trials.

Given widespread use of investigational and off-label products in the NPC community today, it is important to recognize that the existing natural history data is invaluable and may never be replicated. This existing dataset can serve a critical role in supporting future NPC research. Participants discussed the importance of bolstering the available data or utilizing innovative strategies, rather than recreating this dataset, in order to best support NPC therapeutic development.

Given the small population size and global nature of rare disease clinical trials, regulatory advances and collaboration could improve and accelerate drug development and approval for rare diseases like NPC. Collaboration among regulators such as the FDA, the Medicines and Healthcare Products Regulatory Agency, and the European Medicines Agency (EMA) may be of value to support identification of difficult areas and share useful insights. Collaboration can speed up development and refine tools for evaluation. For example, some submissions to EMA have used validated animal models and lessons may be learned by other regulatory bodies from this experience.

Increased or improved feedback mechanisms between regulators and other stakeholders on learnings from failed applications may also help advance therapeutic development for rare diseases like NPC. It is important to learn from what worked well in a given development process, even if a submission for an investigational product didn't achieve regulatory approval, recognizing that there are limitations on the types of information that FDA can share due to restrictions related to confidentiality and proprietary information. Utilizing and building on existing mechanisms, engagement between regulators and patients and caregivers is needed regarding meaningful measurements and acceptable levels of risk for lethal rare diseases. It is important that regulators and other drug development stakeholders understand the risk tolerance and preferences of a given patient population.

There are opportunities for alternatives to traditional clinical trials in NPC therapeutic development, which could improve data and ease burdens on patients. Innovative trial designs that aggregate datasets from multiple study populations, including combining multiple placebo and experimental groups from different drug trials, may help speed NPC therapeutic development. Researchers can learn from existing datasets to help speed NPC therapeutic development; however, stakeholders must work together to increase the availability of existing datasets. Use for more sophisticated statistical models, such as use of multiple N-of-1 models, may better support NPC therapeutic development given the small size and significant heterogeneity of the NPC population.

Of note, rare disease trials often require patients and families to travel significant distances to participate. For patients with complex medical and care needs, any level of travel has the potential to create significant burdens due to patient dietary needs, mobility limitations, other caregiver duties, and more. Decentralized trials or local access to treatment may help to relieve the significant burden of travel for many rare disease patients. Potential application of a hub-and-spoke model for clinical trials may also ease burdens associated with trial participation. Home monitoring capabilities and digital health technologies have advanced over the course of the COVID-19 pandemic. Use of such technologies and practices can be leveraged to make trials more accessible to patients both now and in the future.

Conclusion

During this workshop, it was emphasized that diagnosis of NPC has far-reaching impacts on the lives of patients and their families. While appearing slow and variable in progression from the perspective of

clinical researchers, the effects of NPC can be fast-moving and pervasive for patients. Participants expressed that time becomes the most precious resource that many of these patients have.

Despite the existing challenges in NPC drug development, research on potential therapies and methodologies to assess those therapies is advancing. It is critical to utilize the right measures to assess NPC therapeutics. Measures must be sensitive enough to capture what patients and families are experiencing. Further objective measures could add to the demonstration of clinically meaningful benefit for NPC therapies.

Workshop participants discussed a number of potential strategies for making the NPC drug development process more efficient, including mechanisms of feedback between regulatory agencies, more ongoing collaboration among all stakeholders, and learning from some of the product submissions that have not been successful. Participants highlighted the importance of data-sharing, aggregating existing data, and building on the existing database of patient natural history. Of note, a number of participants emphasized that the existing natural history data are invaluable and not replicable as the treatment paradigm has changed such that many patients are using at least one investigational or off-label product. Throughout the workshop, participants also discussed the importance of having access to care and treatment close to patients' homes and how telemedicine and other methods of decentralization could greatly improve access to trials.

The consensus shared throughout this workshop is that building upon and enhancing existing measures, applying methods and analytics used for assessing treatments in other rare and heterogenous diseases, and continuing to engage all stakeholders – especially patients and caregivers – are essential to facilitating successful drug development for NPC. While not within the scope of this workshop, expanded access to investigational therapies is a topic of interest for many patients and their families. Discussions during this workshop addressed some of the key challenges in NPC drug development, and recommendations and thinking shared by experts throughout the event may provide a helpful foundation for addressing other important challenges impacting progress in this space. Broader conversations will be needed to address the full range of challenges and opportunities for NPC drug development.

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