Niemann-Pick Type C Biomarker/Endpoint Workshop Summary

Niemann-Pick Type C (NPC) is a devastating, ultimately fatal, genetic condition for which there is no cure. In recent years, the NPC community has been discouraged and frustrated by hurdles they have experienced regarding clinical trials and regulatory reviews of candidate therapies in the United States. On May 21, 2022, the Ara Parseghian Medical Research Fund (APMRF) organized the Niemann-Pick Type C Biomarker/Endpoint Workshop to begin a collaborative effort to address these challenges. The workshop was to build upon earlier efforts including a patient-focused drug development (PFDD) meeting in 2019, multiple listening sessions with the FDA in 2021, and a workshop hosted by FDA and the Duke-Margolis Center for Health Policy in January 2022. The goal of this workshop was to bring together scientific, clinical, and regulatory experts to identify potential paths forward that could lead to new, effective therapies for NPC.

The workshop was structured around three themes, described below.

- **Refine U.S. Food and Drug Administration (FDA) and Care Expert Recommendations to improve the NPC Clinical Severity Scale (NPC-CSS):** The NPC-CSS and its predecessors have been used to diagnose NPC, assess disease progression, and measure the effects of candidate therapies for decades. In recent years, however, the FDA has raised concerns about the validity of the NPC-CSS as a measure in clinical trials, especially around inter-rater reliability and the validation of the measure. Discussions during this session were forward-looking and focused on how the NPC-CSS might be improved and validated to address the FDA's concerns while retaining the valuable data that has been generated over many years using this scale. Workshop participants also discussed how clinical outcome assessments (COAs) are developed in general, and whether those best practices can be applied to the community's work in NPC.
- **Identify and Advance Candidate Biomarkers:** At present, the only way to confirm a case of NPC is whole exome sequencing. There are, however, multiple biomarkers that have proven to be helpful in the diagnostic process including measuring levels of oxysterols, lysophingolipids, and/or bile acids. Exploring these and other biomarkers may shed light on potential targets and mechanisms of action for future therapeutics. This session began with a presentation from an FDA representative regarding the process the agency uses to qualify biomarkers for use as drug development tools. Additional presenters spoke about ongoing efforts to identify biomarkers for NPC and how these and other new efforts might be advanced to support drug development.
- **Identify Potential Intermediate Endpoints:** Building on the discussion at the January 2022 workshop hosted by the FDA and Duke-Margolis Center for Health Policy, participants discussed how the community might identify clinical endpoints that could be viable for trials and meaningful to patients and families. Recognizing the challenge of identifying a strong primary endpoint, this session featured presentations on efforts to develop intermediate and composite endpoints – both for NPC and best practices learned from other disease areas. The use of intermediate endpoints, which can be detected earlier than primary endpoints, may also create opportunities for expedited trial processes that help more rapidly deliver therapies to patients.

Discussion topics included both specific endpoints that should be considered as well as approaches the community might take to identify new endpoints.

For each theme, the workshop included presentations from experts on that topic followed by a discussion among group members. At the start of the workshop, moderator Tim Franson, APMRF Director Sean Kassen, and Klaus Romero from the Clinical Path Institute (C-Path) made introductory remarks to set the stage for subsequent discussions. For each of the three themes, workshop participants focused on key action items that could address the major barriers related to that theme. The workshop discussion, including these action items, is summarized below. Additional materials including the workshop agenda and the list of participants are included in the appendices.

Theme 1: Refine FDA and Care Expert Recommendations to Improve the NPC-CSS

This session began with presentations on the development of clinical outcome assessments (COAs), the current status of the NPC-CSS, and ongoing studies to validate the NPC-CSS. In general, workshop participants support the idea of updating the NPC-CSS to align with FDA expectations provided that these updates are conducted in such a way that the years of data collected using the current NPC-CSS remain relevant. With such a small patient population, the trial and observational study data using the NPC-CSS is too valuable to be lost if the field were to shift to the use of a dramatically different COA for NPC therapy development. Workshop participants discussed ways that the NPC-CSS could be refined and opportunities for using a subset of the scale to measure outcomes.

In her presentation on the development of COAs, Dr. Lindsey Murray spoke about the key evidence required for COAs: 1) the conceptual framework or intent of the instrument; 2) evidence that the tool measures what it is intended to measure, known as "content validity"; and 3) evidence of other measurement properties such as reliability, validity, responsiveness, and the ability to link score changes with clinical benefit. Thus far, there is sufficient evidence that the five domains of the NPC-CSS are the key elements that should be measured, but it is not clear that the scale has strong psychometric properties, is relevant for the full NPC age spectrum, and can be used in a standardized way. Workshop participants agreed that the heterogeneity of NPC makes it difficult to find a single measure that will be appropriate for all patients.

Dr. Liz Berry-Kravis, an NPC clinician and researcher, and Dr. Fran Platt, an NPC researcher, presented on the current status of efforts to update the NPC-CSS based on FDA feedback and to validate the instrument. In order to address concerns about the inter-rater reliability of the NPC-CSS, Dr. Berry-Kravis suggested that the community could help develop more standardized clinical evaluation procedures for sites using the measure, including a unified rating guide for all raters and training materials to help families answer questions about their child's NPC-CSS score. Additional qualitative research can be conducted to show that the scale and ratings are viewed similarly across clinician raters. This could be followed by a formal validation study showing fidelity for cases rated by clinician raters. Dr. Berry-Kravis is currently analyzing data from her cohort of patients at Rush and the natural history study cohort at NIH to generate stronger evidence of construct validity based on comparison of NPC-CSS scores to scores on other standardized measures that measure the same construct as each domain of the NPC-CSS. This work can be conducted with measures relevant to different age domains to demonstrate the relevance of the NPC-CSS across the full spectrum of ages and severity of NPC. These improvements could support validation of the NPC-CSS. In her presentation, Dr. Platt also proposed the

use of an annual severity increment score (ASIS) as a way to measure the rates of NPC progression. She noted that this approach has been used successfully in other diseases and could be adapted from the five- or sixteen-domain NPC-CSS. An ASIS-type measure for NPC showing a rate of progression could then be used in routine clinical care to predict the extent of future disability and to assess treatment responses in trials. Both Dr. Berry-Kravis and Dr. Platt noted that more work is needed, but there are opportunities to leverage existing NPC datasets and patient cohorts to support a validated measure.

Workshop participants discussed ways in which the NPC-CSS might be narrowed to yield stronger trial results. Dr. Murray stated that COAs for rare diseases often try to measure too many things or concepts that are unlikely to respond during a trial period. For example, although cognition is important to patients and families, it is extremely difficult to measure over a six-month or one-year trial period. Given the heterogeneity of NPC, workshop participants agreed that different measures may be appropriate, although NPC clinicians in attendance raised concerns with regard to how the use of a narrower measure would impact the potential trial population size when the total number of people with NPC is already quite small. Another participant suggested that if more narrow, easier-to-measure domains were used as primary endpoints, domains like cognition that are very important to people with NPC and their families could be used as a secondary or exploratory endpoint and could be collected for long-term studies in which cognition would be expected to change, so this data could still be collected.

> **Next Steps:** Workshop participants agreed that it would be appropriate to continue ongoing efforts led by Dr. Liz Berry-Kravis to update the NPC-CSS to address the FDA's concerns about the scale. Participants also expressed interest in working with industry partners in a pre-competitive arrangement to inform the selection of COAs and endpoints as well as best practices for leveraging natural history data to enable studies.

Theme 2: Identify and Advance Candidate Biomarkers

The next session began with presentations on the current status of developing biomarkers for NPC and the FDA's program for qualifying biomarkers. As Dr. Abena Agyeman shared in her presentation, the FDA defines a biomarker as "a characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions."[1] Given the challenges of measuring endpoints in NPC, the identification of a surrogate such as a biomarker or an intermediate clinical endpoint could be useful in more quickly measuring disease progression or response to a candidate therapy. Although FDA qualification of biomarkers is not required for those wishing to use biomarkers in therapy development, it provides an opportunity for stakeholders to work with the agency to address specific drug development needs.

There are currently two relatively large cohorts of NPC patients that may offer helpful data for identifying biomarkers: the NIH Natural History/Observational Study managed by Dr. Denny Porter (includes 138 people) and the cohort managed by Dr. Berry-Kravis at Rush University (includes 72 people). Dr. Porter suggested that it may be helpful to consider proteomics, gene expression, lysosomal abnormalities, and lipidomics in order to identify biomarkers. He also urged the community to consider blood-based discovery efforts to try to find a blood marker that does not display the high variability seen

[1] FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource. Silver Spring (MD): Food and Drug Administration (US); 2016-. Glossary. 2016 Jan 28 [Updated 2021 Nov 29]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK338448/ Co-published by National Institutes of Health (US), Bethesda (MD).

thus far, rather than just the cerebrospinal fluid (CSF) markers that are often more consistent in assessing brain changes, given that CSF markers require a lumbar puncture, which is more invasive and often requires sedation for young children.

In general, workshop participants see promise in efforts to identify biomarkers for NPC. During the discussion portion of the session, Dr. Carole Ho from Denali Therapeutics emphasized the value of natural history studies in not only advancing our understanding of biomarkers but also having those biomarkers demonstrate clinical benefit. Some participants noted that it may be necessary to develop an assay to support a biomarker, although others pointed out that it is not always necessary to have a truly quantitative assay and assays do not have to go through the FDA biomarker qualification process. As in the discussion on Theme 1, participants recognized the possible need to focus on certain subsets of the heterogenous NPC population in order to facilitate biomarker development.

> **Next Steps:** Ideally, a core panel of exploratory biomarkers would be promulgated as a mandatory study component for inclusion in all industry clinical trials, to hasten qualification of such tools. In addition, sponsors and academic researchers are encouraged to pursue development of potential new biomarker assays for future exploration. In the near future, a large dataset using mass spectrometry to analyze patient cerebrospinal fluid (CSF) samples from natural history, control, and adrabetadex- and miglustat-treated patients will be provided to researchers for analysis. It will also be important to identify a statistician who can support NPC scientists in analyzing this data.

Theme 3: Identify Potential Intermediate Clinical Endpoints

For the third session, the opening presentations focused on the use of patient preference studies to inform the selection of intermediate or composite clinical endpoints and how we might consider developing those endpoints for NPC. With a disease like NPC where it can take a long time to measure traditional endpoints, the use of intermediate or composite endpoints may offer earlier signals of the likelihood that a treatment is effective and therefore could potentially speed development. Such endpoints can be used in combination with more traditional primary endpoints and can offer useful data that can inform drug development.

Dr. John Bridges from The Ohio State University, a recognized leader in patient preference studies, presented on general approaches and methodology for these studies to help other workshop participants understand how these studies could be helpful for NPC therapy development. These types of studies can provide a structured, quantifiable way to understand what matters most to patients in terms of treatments and how a disease impacts their daily lives. That information can then be used to inform the selection of endpoints for studies of candidate therapies.

Conducting preference studies within the NPC patient and caregiver population may be especially timely as the community is considering whether there may be other ways to focus therapy development efforts. Were researchers and drug developers to consider focusing on a subset of the domains of the NPC-CSS as an endpoint, such studies could inform the domain selection process. Preference studies can also be used to explore patient views on different tradeoffs, such as longer lifespan with more symptoms vs. a shorter lifespan with fewer symptoms. For a disease as heterogenous as NPC,

understanding whether there are consensus views among patients and caregivers could steer therapy development in a direction that accounts for patient priorities.

During the discussion, workshop participants brainstormed potential intermediate endpoints that could be used for NPC therapy development. Dr. Marc Patterson from Mayo Clinic noted that imaging-based endpoints have not been widely explored for NPC but there are examples of studies using imaging to assess cerebellar volume in response to treatment with miglustat, a drug approved in the U.S. for the treatment of Gaucher disease that also is commonly used for NPC. Participants also discussed the possibility of ambulation serving as an intermediate endpoint, with Dr. Bill Pavan from NIH noting that there may be opportunities for the use of GPS-based data to track mobility. Concerns were raised, however, that narrowing the endpoint to a specific area of function could be limiting in terms of enrollment as only those with problems in the chosen area could be enrolled, and due to the heterogeneity of NPC, populations with mainly symptoms in other domains (e.g. cognition vs. ambulation/ataxia) could not be assessed. Another idea suggested was to use a biomarker that is not specific to one domain or organ, as has been done in cancer therapy development.

> **Next Steps:** Workshop participants agreed that it would be helpful to consider ways to develop intermediate or composite clinical endpoints for NPC, and to consider expanded data sharing efforts. There also appears to be interest in using patient preference studies to inform the development and selection of these endpoints.

Wrap-Up and Next Steps

The NPC Biomarker/Endpoint Workshop provided a valuable opportunity for members of the NPC research, clinical, and therapy development communities to come together and identify possible ways to break the current logjam for NPC therapy development. Although the workshop was divided into three themes, it was clear that the themes are highly interconnected and many of the next steps described above will need to be taken in parallel. For example, refining the NPC-CSS to address FDA concerns about the scale will yield a stronger measurement tool that can be used to inform the development of biomarkers and endpoints.

There was consensus among participants that any future actions should be taken with the intention of preserving as much existing data on the NPC population as possible. Community members recognize that data on people who currently have or have already passed away from this rare, fatal disease is precious and should be used to the maximum extent possible to inform future therapy development efforts. This data could include both ongoing natural history studies and observational cohorts as well as findings from past clinical trials.

Participants—including those from the FDA—indicated a desire to work together to address the huge burden of unmet medical need in the NPC population. C-Path has a strong track record of convening multi-stakeholder consortia to tackle therapy development challenges with input from the FDA, industry, and other stakeholders. C-Path participants at the workshop discussed the possibility of conducting a feasibility landscape assessment to determine their bandwidth for establishing the most efficient type of collaboration (either a consortium dedicated to NPC, or a broader public-private partnership for lysosomal diseases, with a dedicated effort in NPC).

This workshop was intended not as a one-off event, but as a foundational way to drive future research and therapy development efforts forward in a positive direction. The next steps outlined in this summary report will serve as an initial roadmap for those efforts. Participants ended the meeting by reiterating their desire to work together to find treatments and, ultimately, a cure for this devastating disease.

Appendix A: Workshop Agenda

NPC Biomarker/Endpoint Workshop

Saturday, May 21, 2022 | 8:00 a.m. to 12:15 p.m.
The Westin La Paloma | Tucson, AZ

Agenda

8:00 am – 8:15 am **Welcome and Introductions**
Tim Franson, MD, Moderator
Faegre Drinker Consulting

8:15 am – 8:25 am **Why we are Here and Goals of Initiative**
Sean Kassen, PhD
Ara Parseghian Medical Research Fund, University of Notre Dame

8:25 am – 9:25 am **Theme 1: Refine FDA and Care Expert Recommendations to Improve NPC-CSS**

Presentations and Speakers:

8:25 am – 8:35 am
Overview of Clinical Outcome Assessments
Lindsey Murray, PhD, MPH
Rare Disease Clinical Outcome Assessment (COA) Consortium, Critical Path Institute

8:35 am – 8:45 am
Overview of Current Status of NPC-CSS and FDA's Desired Outcomes
Elizabeth Berry-Kravis, MD, PhD
Rush University Medical Center

8:45 am – 8:50 am
Update on Validation Studies
Fran Platt, FRS FMed Sci
University of Oxford

8:50 am – 9:25 am
Group Discussion

9:25 am – 9:35 am **Break**

9:35 am – 10:35 am Theme 2: Identify and Advance Candidate Biomarker(s)

Presentations and Speakers:

9:35 am – 9:45 am
Overview of Qualifying Biomarker(s)
Abena Agyeman, PhD
U.S. Food and Drug Administration

9:45 am – 9:55 am
Current Status of Biomarker(s) in NPC
Denny Porter, MD, PhD
National Institute of Child Health and Human Development

9:55 am – 10:35 am
Group Discussion

10:35 am – 11:35 am Theme 3: Identify Potential Intermediate Endpoints

Presentations and Speakers:

10:35 am – 10:50 am
Overview of Intermediate and Composite Endpoints
John Bridges, PhD
Johns Hopkins Bloomberg School of Public Health

10:50 am – 11:00 am
Overview of Intermediate Endpoints for NPC
Marc Patterson, MD
Mayo Clinic

11:00 am – 11:35 am
Group Discussion

11:35 am – 12:15 pm Open Discussion and Wrap-Up (working lunch)

Appendix B: Workshop Participants

First Name	Last Name	Title	Organization
Abena	Agyeman	Senior Biologist	Food and Drug Administration
Elizabeth	Berry-Kravis	Professor and Co-Director, Molecular Diagnostics Section of Genetic Laboratory	Rush University Medical Center
Alex	Bétourné	Scientific Director for the Rare Disease Cures Accelerator-Data and Analytics Platform	Critical Path Institute
Lauren	Bloch	Director	Faegre Drinker Consulting
John	Bridges	Professor in the Departments of Biomedical Informatics and Surgery	The Ohio State University
Stephanie	Cologna	Associate Professor	University of Illinois Chicago
Tim	Franson*	Principal	Faegre Drinker Consulting
Carole	Ho	Chief Medical Officer and Head of Development	Denali Therapeutics
Justin	Hopkin	Chairman of the Board Chief, Division of Hospital Medicine	National Niemann-Pick Disease Foundation Strong Memorial Hospital
Sean	Kassen	Director	Ara Parseghian Medical Research Fund
Joe	Lamendola*	Senior Director	Faegre Drinker Consulting
Lindsay	Murray	Executive Director, Rare Disease Clinical Outcome Assessment Consortium	Critical Path Institute
Dan	Ory	Chief Medical Officer	Casma Therapeutics
Cindy	Parseghian	President	Ara Parseghian Medical Research Fund
Marc	Patterson	Professor and Chair, Child and Adolescent Neurology	Mayo Clinic
Bill	Pavan	Senior Investigator, National Human Genome Research Institute	National Institutes of Health
Fran	Platt	Professor, Head of Pharmacology Department	University of Oxford
Denny	Porter	Senior Investigator, Program Head, Clinical Director	National Institutes of Health
Melissa	Raspa	Senior Research Public Health Analyst	RTI International
Klaus	Romero	Chief Scientific Officer	Critical Path Institute
Sudhir	Sivakumaran	Vice President, Neuroscience Program	Critical Path Institute
Beth	Solomon	Senior Lead, Speech-Language Pathologist	National Institutes of Health

First Name	Last Name	Title	Organization
Kristen	Swingle	Interim President and Chief Operating Officer	Critical Path Institute
Anne	Wheeler	Research Public Health Analyst	RTI International

*Moderators