



FDA Listening Session on Niemann-Pick Disease

SUMMARY REPORT

APRIL 9, 2021

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EXECUTIVE SUMMARY

On April 9, 2021, the leadership of the National Niemann-Pick Disease Foundation and several members of the Niemann-Pick disease community met with members of the FDA in a “Listening Session” with several very important goals:

- Discuss the complex nature of both Niemann-Pick type C and acid sphingomyelinase deficiency (ASMD or Niemann-Pick types A and B) and provide insight into how these complexities impact efforts in both clinical research and patient management.
- Outline the barriers to developing and accessing disease modifying therapies.
- Identify and assess workable strategies to expedite clinical research and provide patients with access to urgently needed treatments.

In presentations by NNPDF executive director Joslyn Crowe, several leading clinicians and patient advocates, the program highlighted many aspects of the severe and devastating impact of Niemann-Pick disease on patients, caregivers and communities. Participants also highlighted the patient community’s dedication to supporting clinical research. The speakers emphasized that the lack of an approved therapy continues to put members of this community at unnecessary risk of decline and death.

In the program, NNPDF also outlined five areas of action that we hope the FDA and the broader research and treatment communities will support moving forward:

1. We strongly encourage the FDA and leaders in clinical research to consider and accept the design of novel clinical trials that use natural history and in-person analysis to limit the need for placebo controls in clinical trials.
2. We call for the broader use of “conditional approval” pathways with study designs that support drug approvals with requirements for ongoing long-term post-approval monitoring of safety and effectiveness. This approach can address the challenges in clinical research in a heterogeneous disease that has highly variable progression.
3. We hope the FDA will support the development of therapies positioned to address different aspects of Niemann-Pick Disease with the potential to transform it into a chronic disease. Currently, there are four agents in the later stages of clinical development that appear to be safe and efficacious based on community experience in clinical trials. We ask the Agency to consider the patient experience in addition to clinical data in the review for approval of these agents.
4. Based on extensive experience with off label use of miglustat to treat NP-C, work to identify strategies that can help patients maintain access to this therapy as we also try to find an expeditious route for approval of miglustat in NP-C.
5. Support continued EAP access to adrabatadex and rapidly identify a strategy to move this program forward. We would like to schedule a follow-up meeting where NP-C families can share their positive experiences with adrabatadex.

We are very grateful for the opportunity to share our perspectives with the FDA and hope you will reach out to us at any time when we can provide additional information that supports your important work. In many of the issues we have raised, there is a clear sense of urgency in the need to take action that can support patients and families. We look forward to continuing this important dialogue.

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Agenda

Goals:

1. Discuss the complex nature of both Niemann-Pick Type C and Acid Sphingomyelinase Deficiency (Niemann-Pick Types A and B)
2. Discuss the current barriers our community faces in developing and accessing disease modifying therapies
3. Propose suggestions to expediently provide patient access to urgently needed treatments for both ASMD and NP-C

This meeting is not intended to replicate the PFDD that took place in March 2019 but to elevate awareness of the acute issues faced by the Niemann-Pick community - families, clinicians, and industry

Agenda:

1. Welcome

Shawn Brooks, Professional Affairs & Stakeholder Engagement (PASE), Center for Drug Evaluation and Research (CDER), Office of the Center Director (OCD)

Dr. Patrizia Cavazzoni, Acting Director, Center for Drug Evaluation and Research; Deputy Center Director for Operations, Center for Drug Evaluation and Research (CDER)
Dr. Peter Stein, Director, Office of New Drugs

2. Brief Introductions 5 minutes

Joslyn Crowe, NNPDP Executive Director
Dr. Justin Hopkin, NNPDP Board Chair

3. ASMD 10 minutes

Overview and access challenges:

Dr. Melissa Wasserstein, Chief, Division of Pediatric Genetic Medicine, Department of Pediatrics, Montefiore Medical Center

Patient Voices:

Sandy Cowie, President, International Niemann-Pick Disease Alliance (INPDA), ASMD patient

- Burden of disease, costs of delays
- Impact on global community

Taylor Sabky, Parent of Purnell Sabky

- Unmet need in NP-A, NP-AB

4. **Niemann-Pick Type C (NPC)** 30 minutes

Overview:

Dr. Caroline Hastings, UCSF Benioff Children's Hospital Oakland

Challenges with trial design for ultra-rare disease and ethics and acceptability of placebo in fatal neurological disease:

Dr. Marc Patterson, Chair, Division of Child and Adolescent Neurology, Mayo Clinic

Patient Voice:

Cara Gilmore, NPC Patient

- Quality of life with NPC, concerns about clinical trial design
- Perspective on participating in placebo trials

Natural history study data:

Dr. Forbes Porter, Senior Investigator & Clinical Director, National Institutes of Health

Access to therapies:

Dr. Elizabeth Berry-Kravis, RUSH University Medical Center

Patient Voices:

Rebecca Spencer White, Parent of Johnathan

- Reality of loss of access to investigational therapy with observed benefit

Sara Peterka, Parent of Emma

- Difference made by early intervention in short period of time

Denise Miller, Parent of Woodrow

- Urgency for access to investigational therapies

NNPDF and Niemann-Pick Community Recommendations

5. **Discussion** 15 minutes

6. **Summary**

Dr. Hylton Joffe, Director, Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine (ORPURM)

7. **Closing Remarks**

Dr. Patrizia Cavazzoni, Acting Director, Center for Drug Evaluation and Research; Deputy Center Director for Operations, Center for Drug Evaluation and Research (CDER)

Participants

Dr. Elizabeth Berry-Kravis, RUSH University Medical Center

Shawn Brooks, Professional Affairs & Stakeholder Engagement (PASE), Center for Drug Evaluation and Research (CDER), Office of the Center Director (OCD)

Dr. Patrizia Cavazzoni, Acting Director, Center for Drug Evaluation and Research; Deputy Center Director for Operations, Center for Drug Evaluation and Research (CDER)

Sandy Cowie, President, International Niemann-Pick Disease Alliance (INPDA), ASMD patient

Joslyn Crowe, NNPDP Executive Director

Cara Gilmore, NPC Patient

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Dr. Forbes Porter, Senior Investigator & Clinical Director, National Institutes of Health

Taylor Sabky, Parent of Purnell Sabky

Rebecca Spencer White, Parent of Johnathan

Dr. Peter Stein, Director, Office of New Drugs

Dr. Melissa Wasserstein, Chief, Division of Pediatric Genetic Medicine, Department of Pediatrics, Montefiore Medical Center



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April 9, 2021 | 2:00 pm EST

» Welcome

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Dr. Patrizia Cavazzoni, Acting Director, Center for Drug Evaluation and Research; Deputy Center Director for Operations, Center for Drug Evaluation and Research (CDER)

Dr. Peter Stein, Director, Office of New Drugs

▶▶ Introductions

Joslyn Crowe, Executive Director, National Niemann-Pick Disease Foundation

Dr. Justin Hopkin, Board Chair, National Niemann-Pick Disease Foundation

Opening Statement

Joslyn Crowe, NNPDP Executive Director



Good afternoon. I'd first like to thank the FDA for hosting this Listening Session. We are honored to have so many Departments and colleagues here today.

NNPDF is the national patient organization for Niemann-Pick Diseases, focused on patient advocacy, family supports, and research. For nearly 30 years, NNPDP has served families throughout the nation at all stages of their Niemann-Pick journey.

Today we are bringing together expert clinicians, patients, devoted families & stakeholders from all parts of the NP community to express the urgency felt on multiple issues across these diseases. We hope this will be the start of several discussions and collaborative actions.

We thank you for your work with our sponsors to submit and review applications. A lot of focus today is about creating pathways for moving forward and that is because we are confident that the current therapies in review will be the first approved for our patients.

We have one overarching request – help us to help our patients get the medicines that they urgently need. You'll hear today that our families have waited a long time to be at the place we are now—with therapies nearing approvals—and we've lost too many Niemann Pick patients while waiting.

We ask that you hear our need to make and bring treatments that are safe and effective to our patients and help us gain approvals for what we have now. Help us by approving what exists today and also to bring more options to the table for our families. Our dream is for NP patients to have the ability to make decisions with their physicians about what will work best for each patient and will improve their quality of life.

This is a community though without the time to wait further. As one parent recently told me, "This is a matter of keeping our loved ones alive. Nothing less".

Now I'd like to introduce Dr. Justin Hopkin, NNPDP's Board Chair.

▶▶ Goals

- Discuss the complex nature of both Nieman-Pick Type C and Acid Sphingomyelinase Deficiency (Niemann-Pick Types A and B)
- Discuss the current barriers our community faces in developing and accessing disease modifying therapies
- Propose suggestions to expediently provide patient access to urgently needed treatments for both ASMD and NP-C

This meeting is not intended to replicate the PFDD that took place in March 2019 but to elevate awareness of the acute issues faced by the Niemann-Pick community - families, clinicians, and industry

▶▶ Acid Sphingomyelinase Deficiency (Niemann-Pick Types A and B)

Dr. Melissa Wasserstein, Chief, Division of Pediatric Genetic Medicine,
Department of Pediatrics, Montefiore Medical Center

Dr. Melissa Wasserstein

Chief, Division of Pediatric Genetic Medicine, Department of Pediatrics,
Montefiore Medical Center

Acid sphingomyelinase deficiency (ASMD) is a rare, debilitating lysosomal storage disease caused by pathogenic variants in the *SMPD1* gene. Deficient activity of lysosomal enzyme acid sphingomyelinase (ASMD) leads to sphingomyelin accumulation in various organs including the lung, liver and spleen. Although historically linked, ASMD is genetically, medically and biochemically a distinct disorder from NP-C.



ASMD is a spectrum of disease, with the most severe form being **infantile neurovisceral** ASMD (previously known as Niemann-Pick type A). This form of the disease is seen early in infancy leading to death by age three and is characterized by severe visceral disease and neurodegeneration. The intermediate phenotype is **chronic neurovisceral** ASMD (previously known as Niemann-Pick Type A/B). Onset ranges from infancy to childhood with death occurring in childhood to mid-adulthood. This form of the disease is more slowly progressive than type A with variable visceral disease and neurodegeneration. We often see developmental delay, ataxia, and neuropathy in this intermediate phenotype. The attenuated phenotype is **chronic visceral** ASMD (previously known as Niemann-Pick Type B). This form of the disease is slowly progressive with variable visceral disease and little to no neurologic involvement. Death can occur from childhood to late adulthood.

Olipudase alfa is an enzyme replacement therapy in clinical development for non-central nervous system manifestations of ASMD in children and adults. The first of five clinical trials in humans for olipudase began in 2006. The most recent studies demonstrate statistically significant improvements in diffusion capacity of the lungs, reduction in spleen volume and reduction in liver volume. There were not significant safety concerns reported in the pediatric or adult trials. There is no FDA-approved therapy for ASMD and the community has been anxiously awaiting access to olipudase for 15 years.

It should be noted that olipudase alfa in the IV form does not cross the blood brain barrier and will not impact the central nervous system manifestations of ASMD. In other lysosomal storage diseases, researchers have evaluated gene therapy, intrathecal ERT, bone marrow transplant and small molecule therapies for treatment of neuronopathic manifestations. Unfortunately, there are no therapies near clinical trial readiness for the neurologic manifestations of ASMD. If olipudase is approved, the treatment of neuronopathic manifestations will be the most significant unmet need within the ASMD community.

Therapy for Acid Sphingomyelinase Deficiency: Overview and Unmet Needs

Melissa P. Wasserstein, MD
Chief, Division of Pediatric Genetic Medicine
Children's Hospital at Montefiore
Professor, Pediatrics and Genetics
Albert Einstein College of Medicine



THE PEDIATRIC HOSPITAL FOR:

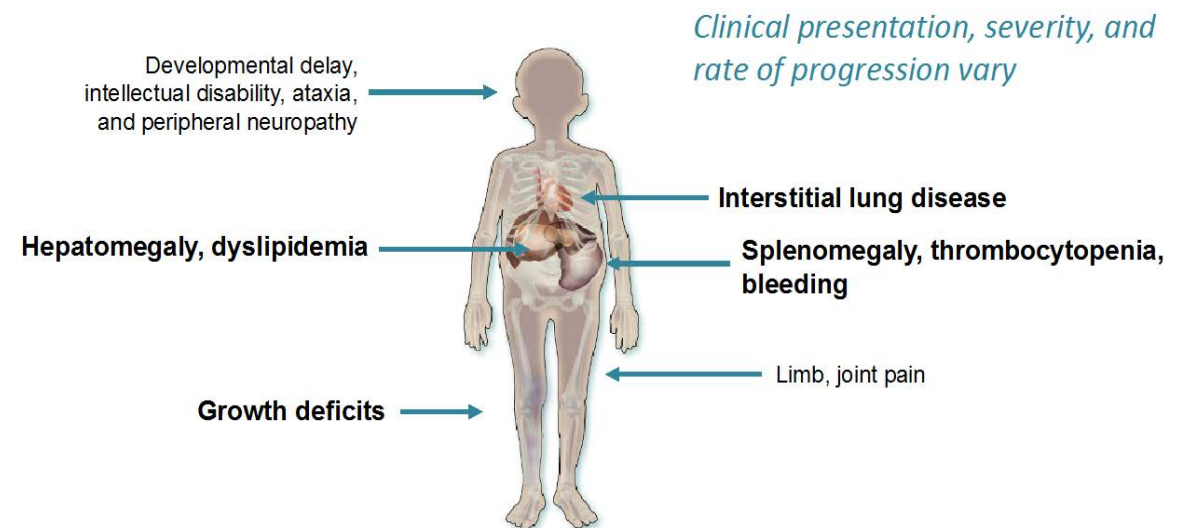


Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Acid Sphingomyelinase Deficiency (ASMD)

- Rare, debilitating lysosomal storage disease
- Caused by pathogenic variant(s) in *SMPD1* gene
- Deficient activity of lysosomal enzyme acid sphingomyelinase (ASM) leads to sphingomyelin accumulation in various organs
- Although historically linked, ASMD is genetically, medically, and biochemically a distinct disorder from Niemann Pick C

Clinical Manifestations of Chronic ASMD (Type B and A/B) in Children



Clinical Spectrum of ASMD

Clinical spectrum



Severe phenotype

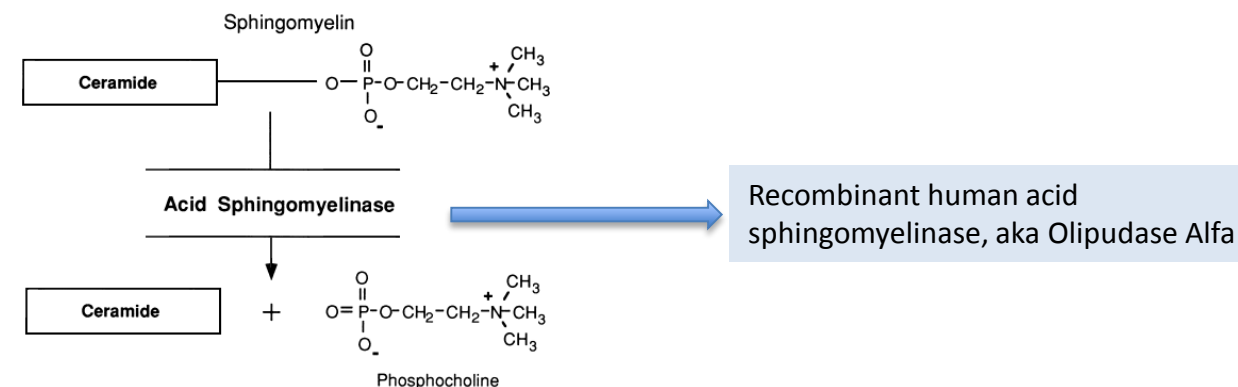
Intermediate Phenotype

Attenuated phenotype

	Infantile neurovisceral ASMD (NPD A)	Chronic neurovisceral ASMD (Intermediate NPD; NPD A/B; NPD B variant)	Chronic visceral ASMD (NPD B)
Onset	Early infancy	Infancy to childhood	Infancy to adulthood
Phenotype	Rapidly progressive, severe visceral disease and neurodegeneration	Slowly progressive, variable visceral disease and neurodegeneration that includes developmental delay, intellectual disability, ataxia, and peripheral neuropathy	Slowly progressive, variable visceral disease with little or no neurologic involvement
Life expectancy	Death by age 3	Death from childhood to mid-adulthood	Death from childhood to late adulthood



Olipudase alfa clinical trials



- An enzyme replacement therapy in clinical development for non-central nervous system manifestations of ASMD in children and adults
- History
 - NCT00410566 Safety Study of rhASM Enzyme Replacement Therapy in Adults With Acid Sphingomyelinase Deficiency
 - NCT01722526 Tolerability and Safety Study of Recombinant Human Acid Sphingomyelinase in Acid Sphingomyelinase Deficiency Patients
 - NCT02004704 A Long-Term Study of Olipudase Alfa in Patients With Acid Sphingomyelinase Deficiency
 - NCT02004691 Efficacy, Safety, Pharmacodynamic, and Pharmacokinetics Study of Olipudase Alfa in Patients With Acid Sphingomyelinase Deficiency
 - NCT02292654 Safety, Tolerability, PK, and Efficacy Evaluation of Repeat Ascending Doses of Olipudase Alfa in Pediatric Patients <18 Years of Age With Acid Sphingomyelinase Deficiency

2006

2021

Olipudase alfa clinical trial outcome

- Primary endpoints were met
 - Statistically significant improvements in DLCO, spleen volume, and liver volume
- No significant safety concerns



Neuronopathic ASMD: *Unmet Need*

- Intravenous olipudase alfa does not cross the blood brain barrier so will not impact the central nervous system manifestations of ASMD
- Approved therapies, clinical trials, and other therapeutic interventions for neuronopathic lysosomal storage disorders
 - Gene therapy
 - Intrathecal ERT
 - Bone marrow transplant
 - Small molecule therapies
- There are no therapies near clinical trial readiness for ASMD type A

▶▶ Patient Voices

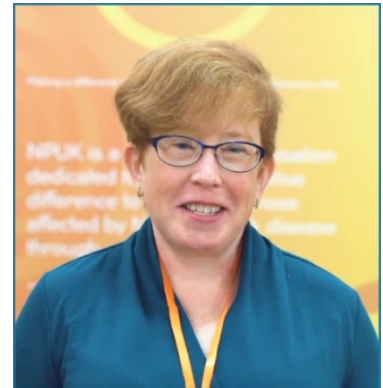


Sandy Cowie

President, International Niemann-Pick Disease Alliance (INPDA),
ASMD Patient

Sandy Cowie

President, International Niemann-Pick Disease Alliance (INPDA);
ASMD Patient



Thank you for the opportunity to speak to you today.

As you know there is no currently approved treatment for ASMD. There is one agent currently in trial and this has been a very long process to get to the point it is at present. This treatment has been the hope on the horizon for more than 20 years. It has been almost 15 years since the initiation of the initial safety trial. When discussing a progressive disease with no other treatment options this is a very long time. It has felt like a carrot on a stick but the stick has been getting longer and the reward further and further away. I recognize the need for safety and ensuring appropriate oversight but time and delays have costs for our community. With a disease with a variable rate of progression and decline time is not on our side. Over the time that this trial has been in progress I have lost many friends who passed away due to the disease and its complications and continue to watch as members of the community and my own health status continues to decline. As this is a multi-system disease I am encountering increasing shortness of breath, increasing fatigue and new cardiac complications. This has meant being able to spend less time with family and friends, being unable to be an active part of my nephew's lives in the way I was able to be with my nieces 10-15 years ago and adjusting my own expectations of what I can realistically do. Increasingly there is a feeling that the clock is running out for me and I desperately want to see that not be the case for those who follow behind me on this journey with ASMD. And the time pressure is even more significant in NPD type A.

There is a need in such an ultra-rare disease to look at novel approaches that will facilitate recruitment and completion of trials. Although placebo controlled trials with stringent inclusion criteria are the gold standard, in a small community with a variable disease these criteria are difficult to meet and can prolong the recruitment process, and the ask from patients and families in terms of time, commitment, travel are very high. Although many are able to do whatever it takes to access a novel therapy when there is no alternative we need to strive to make it less burdensome.

As the president of the INPDA I also want to highlight that the decisions of the FDA regarding trial design and regulatory approvals have global impact especially when trials need to be multicenter, multinational to recruit adequate patient enrollment.

►► Patient Voices

Taylor Sabky

Parent of Purnell Sabky, ASMD



Taylor Sabky

Mother of Purnell, ASMD Type A (In Memory)

My name is Taylor Sabky; I am the proud mother of Purnell, who passed away just over a year ago from ASMD or Niemann-Pick Type A.

I'd like to tell you briefly about Purnell's impressive 44 months on this earth when dealing with a terminal illness. That's how we measured time, in months not years. Our firstborn, Purnell made dreams come true for me and my husband Sam. He was sweet and gentle; he was joyful; he loved life. He brought people together and taught us monumental lessons we will never forget.

At his peak, he was happy and observant, smiled and laughed often, made sounds, reached for toys, could briefly sit up unassisted, could eat pureed foods, and drink from a sippy cup. But that's as far as he developed. From there it was only decline. He was never able to eat solid food that wasn't pureed, he never walked or crawled, he never said "mama" or "dada" or any other word. There are many milestones he never met.

His nursery was set up like a hospital unit - equipment, monitors, medication, even staffed with nurses. For a significant portion of his life, he was connected to one tube or another. I couldn't pick up my son without also carrying a feeding pump, oxygen, BiPAP or any combination of those things. I had getting in and out of the car for appointments down to a science. I rarely think of Nell's life with a deficit lens, but I think it's important to appreciate that while he lived to almost 4 years old, Nell was far from a typical 4-year-old. This is not a quality of life to be aspired to.

Purnell was diagnosed on May 12, 2017, days before Mother's Day. We sat in Dr. Wasserstein's office as she confirmed Type A and told us our options... none. "Go home and love your kid" is the advice that families receive when they get the diagnosis of Type A.

We were told of treatments in clinical trial for other forms of the disease. But for Type A, research was being conducted - and is ongoing to this day - but nothing is close to moving from the lab to the clinic. Our prospects are the same as they were 4 years ago when we sat in Dr. Wasserstein's office. And I can tell you the names of all the kids who have been born, diagnosed and passed from Type A in that same span.

I am THRILLED by the success of the olipudase alfa program, but this treatment could not help my son. Type A affects the brain, and there is no evidence that olipudase alfa would cross the blood-brain barrier or have any impact on the neurologic involvement for Type A and Type A/B patients. Without increased efforts in treatment development for ASMD, our children will continue the course of Type A. And our community deserves more than that. Our children deserve a chance to live. Our families deserve a chance for hope.



▶▶ Niemann-Pick Type C (NPC)

Dr. Caroline Hastings, UCSF Benioff Children's Hospital Oakland

Dr. Caroline Hastings

President, UCSF Benioff Children's Hospital Oakland



- NPC is an ultra-rare, pan-ethnic inherited disease inherited in an autosomal recessive manner. It's a neurovisceral disorder of lipid storage and trafficking, leading to accumulation of unesterified cholesterol in cellular compartments leading to dysfunction and cell death.
- NPC is characterized by progressive neurologic deterioration and organ dysfunction.
- Timing of symptom onset, clinical stigmata and rate of progression are highly variable, contributing to challenges in recognition and diagnosis.
- Prevalence 1:120,000-150,000, though likely much higher incidence due to diagnostic difficulties.
- At this time, there is no curative therapy for NPC, nor is there any FDA approved disease modifying treatment.
- Over 500 mutations have been identified, leading to problems in the NPC protein, and this explains in part the extreme variability of the clinical presentations.
- The majority of mutations are in the NPC1 protein (95%) and 4-5% of mutations are in the NPC2 gene. These proteins together are involved in the efflux of cholesterol from the lysosomes and mutations lead to protein dysfunction, build up and cascade of deficits leading to cellular death.
- There is no phenotypic-genotypic correlation, though missense mutations appear more often in the older patients and loss of function and frameshift mutations in younger patients with more severe forms of the disease. However, even within families, siblings may manifest different symptoms with different timing of onset of symptoms.
- There is a highly variable onset of symptoms throughout a patient's lifespan, including neurologic, systemic and psychiatric signs and symptoms. No 2 patients are the same, and no single outcome applies to all. The combination of disease manifestations contributes to poor quality of life and premature death.
- There is an extreme variability in symptoms onset from infancy through late adulthood. Infants primarily have systemic disease and may have severe cholestatic jaundice and severe liver disease with early mortality. Early and late infantile, and juvenile onset show primarily neurocognitive manifestations with progression, and adolescents/adults may have psychiatric symptoms and a movement disorder, and possible early dementia.
- Much has been learned over the past decade in understanding the nature of the disease, and clinical innovations to address the complexity of the disease have led to drug candidates for intervention. Some of these have completed trials, others are continuing at this time.
- A trial of arimoclomol, an inducer of heat shock protein 70, has been completed, and results in children are encouraging. The drug application is currently with the FDA.
- Intravenous hydroxypropyl-beta-cyclodextrin, TrappsolCyclo, has completed phase I and II trials, and with encouraging safety and clinical outcomes data, is now poised to start a phase III trial this spring.

- Intrathecal hydroxpropyl-beta-cyclodextrin, adrabetadex, completed phase I/II trials, and is still in expanded access with individual patient INDS through Oct 2021 pending institutional approval, and the clinical development program has been cancelled.
- Acetyl-L-leucine has shown benefit in ameliorating neurologic symptoms in NPC in open label studies and a phase II trial has been completed.
- There is clinical consensus that a combination approach may be beneficial in some patient sub-sets and may include some of these recently trialed drugs as well as miglustat, and other future therapies including S1P5 receptor agonists and/or gene therapy.

Niemann-Pick Type C

- Pan-ethnic, autosomal recessive *neurovisceral* lipid storage and trafficking disorder characterized by the accumulation of unesterified cholesterol and other lipids within the late endosomal/lysosomal compartment of all cells in the body
- Clinically characterized by progressive neurologic deterioration and organ dysfunction
- Many patients have splenomegaly in combination with neurologic and/or psychiatric manifestations
- Apparent timing of onset of disease and rate of progression highly variable
- Prevalence of 1 in 120,000-150,000; actual incidence may be higher, frequently unrecognized, and under- and mis-diagnosed

There is **no curative therapy** for Niemann-Pick Type C, nor is there any FDA-standard approved disease modifying treatment.



Molecular genetics of NPC

Gene symbol	Chromosomal locus	Frequency (mutations)	Protein size
<i>NPC1</i>	18q11–q12	90 – 95% of cases (sequence alterations) > 250 <i>variants</i>	1278 amino acids (transmembrane protein)
<i>NPC2</i>	14q24.3	4% of cases (sequence alterations) > 5 <i>variants</i>	132 amino acids (soluble protein)

- Mutations encoding either NPC1 (95%) or NPC 2 (5%) proteins result in deficiencies/dysfunction, affecting cholesterol transport and metabolism
- **No phenotype-genotype correlation:** Missense mutations often in older patients and loss of function mutations/frameshift in younger more severe forms (null mutations)
- 3 genetic isolates:
 - French Acadians from Nova Scotia; Spanish Americans in Southern Colorado; Bedouin groups in Israel, consanguinity

Adapted from Patterson. *Gene reviews* 2007

NPC: clinical manifestations

■ Neurologic

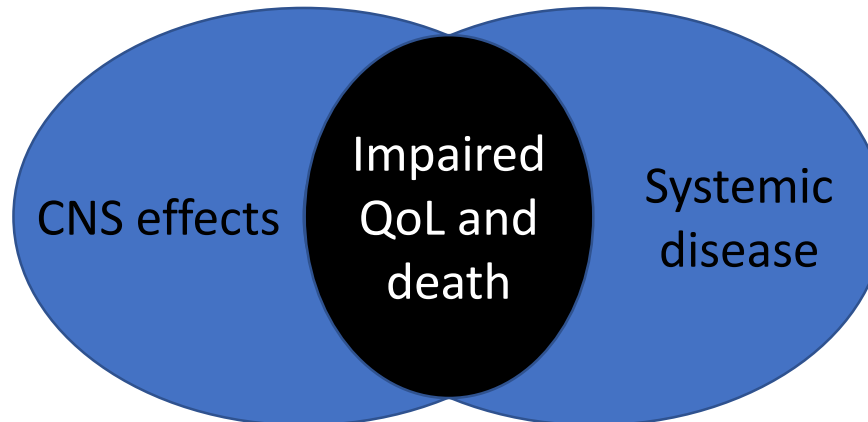
- Developmental delay/loss of milestones
- Impaired motor function
- Behavioral disturbance
- Loss of cognition, memory
- Seizures, cataplexy
- Vertical Supra-nuclear Gaze Palsy (VSGP)

■ Systemic

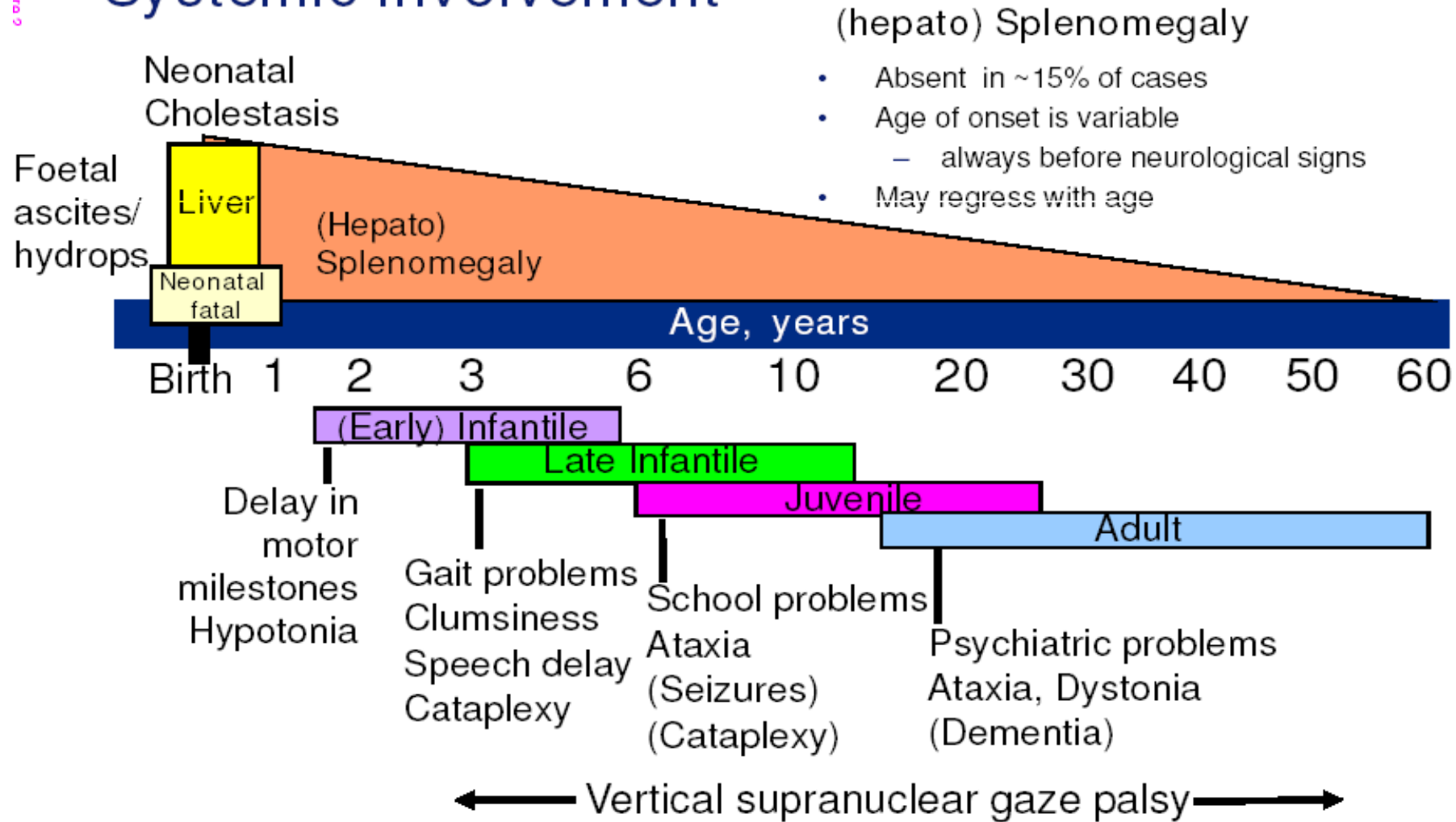
- Prolonged neonatal jaundice
- Liver disease and failure
- Hepatomegaly
- Splenomegaly
- Respiratory dysfunction

■ Psychiatric

No two patients are the same: No single outcome applies to all



Systemic involvement



(hepato) Splenomegaly

- Absent in ~15% of cases
- Age of onset is variable
 - always before neurological signs
- May regress with age

Neurological involvement

Potential Future Therapies

- Trial of [Arimoclomol](#), induces expression of HSP70, showed slowed disease progression over 1 year in children; drug application with FDA, expected summer 2021
- [IV HP \$\beta\$ CD Trappsol[®]Cyclo[™]](#): completed Phase I/II trials in patients with systemic and neurologic sx; pivotal Phase III trial in children and adults to open Spring 2021
- [IT HP \$\beta\$ CD, Adrabetadex](#): completed Phase I/II trials, in expanded access/iINDs through Oct 2021, contingent on institutional approval; Clinical development program cancelled
- [Acetyl-L-Leucine](#) has shown benefit in ameliorating neurologic sx in NPC in open label studies. A Phase II trial has been completed.
- *Trial eligibility varies* (age, severity, presence of certain features, etc.) which impacts outcomes
- **Combination approaches**
 - HSP70 (misfolded proteins) inducer (Arimoclomol)
 - Substrate reduction therapy ([Miglustat](#))
 - Cholesterol trafficking drug (IV HP β CD; IT HP β CD)
 - Sphingosine 1-Phosphate-5 receptor agonist, Phase I trial completed
 - Acetyl-L-leucine
 - Gene therapy

- ▶▶ Challenges with trial design for ultra-rare disease
- ▶▶ Ethics of placebo in fatal neurological disease

Dr. Marc Patterson, Chair, Division of Child and Adolescent Neurology,
Mayo Clinic

Dr. Marc Patterson

Chair, Division of Child and Adolescent Neurology, Mayo Clinic

Thank you for the opportunity to participate.

I would like to introduce and focus on the concept of finite pools.

The first finite, shrinking, pool comprises the patients who are eligible and willing to participate in clinical trials. Although we do not know exact numbers, we suspect that there are 200-300 patients in the United States with Niemann-Pick disease type C. This patient pool comprises a very broad range of ages, manifestations and rates of progression. Owing to the pronounced heterogeneity of this disorder, assembling cohorts of patients whose age, manifestations, and progression rates are sufficiently similar to permit the design and execution of traditional double-blind, randomized controlled trials has always been challenging. The trials that have been discussed earlier have, with difficulty, typically recruited 40 or 50 patients in order to be sufficiently powered to detect effects over 1-2-year period.

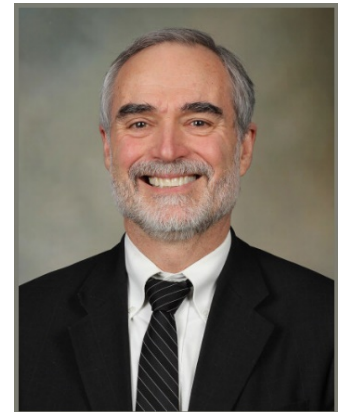
In April of 2021, with multiple clinical trials in progress, and several large, and growing, expanded access programs, the pool of potential participants for new, traditional clinical trials has shrunk to the point where they are no longer feasible.

The second finite, shrinking, pool is that of neurons. All of us have a finite pool of neurons at birth, but those of us who enjoy good health have sufficient reserve capacity to maintain normal neurologic function in the face of physiologic attrition of this neuronal pool. The attrition rate is dramatically increased in patients with Niemann-Pick disease type C patients. The emergence of the first neurologic symptoms of this disease marks the loss of reserve capacity in the relevant neuronal populations. Some of the remaining neurons are malfunctioning, and potentially susceptible to rescue, but the remainder, likely the majority, have been irreversibly lost. In the youngest patients with this disease, those in whom we have the best opportunity demonstrate disease modifying effects over a period of 1-2 years, allocation to the placebo group of a randomized controlled clinical trial guarantees progression of irreversible disease. The same consideration applies to all patients with this disorder, but with a different rate of progression for each affected individual. It is my belief that it is no longer ethical to require placebo controls under these circumstances.

The third finite pool is the data concerning disease progression and the effects of agents which have been studied. These data sets, while imperfect, are precious resources to this community and they reflect the real-life experiences of those afflicted by this disease. They can never be replicated or replaced.

In April of 2021, it is neither feasible nor ethical to propose traditional randomized controlled clinical trials in Niemann-Pick disease type C. This community needs a path by which to use the resources we have, combined with non-traditional trial designs, to ensure continuing access to potential therapies, while we continue to learn how their combination will best benefit individual patients, while ensuring their safety.

Thank you



▶▶ Patient Voices



Cara Gilmore
NPC Patient

Cara Gilmore

NPC Patient

Hello. I'm Cara Gilmore. I'm 42 and live in Pittsburgh, PA. I was diagnosed with NPC in September 2019, after a misdiagnosis of Spinocerebellar Ataxia and an 18-month diagnostic journey. I am lucky to be able to work from home full time as a Learning Strategist. Most of my symptoms are ataxic. I walk with a rollator, and have slowed speech, difficulties with fine motor skills, and intention tremors.



After my diagnosis, I researched potential clinical trials to enroll in. I was concerned because the trials required that I go off of a medication that I was taking to help manage the progression of my ataxia. Since the trials used placebos, and were year or longer, I was concerned that I would participate in the trial, only to be given the placebo, and in a year or two, my condition would progress, without any treatment.

Patients living with NPC don't have the time for lengthy trials with placebos. I acknowledge that the placebo patients help to prove efficacy, but because NPC is so variable, no one progresses the same, nor even has the same symptoms. Customizing trial design for NPC patients would benefit patients and caregivers, giving us peace of mind, that we may avoid progression, as we explore potential treatments and cures.

I am most concerned that there are no approved medications yet for NPC patients. I've come to learn that even just no progression is a win with NPC. There isn't a perfect solution for everyone. I'm very focused on improving the quality of my life, looking for treatments, and potential cures, that are not worse than the disease itself, and improve whatever time I may have left. As an NPC patient, we need to have as many medical options available to us as possible. We are in desperate need, and there is no time like the present.

▶▶ Natural History Data

Dr. Forbes Porter, Senior Investigator & Clinical Director,
National Institutes of Health

Dr. Forbes Porter

Senior Investigator & Clinical Director, National Institutes of Health

This afternoon I would like to illustrate and reinforce a number of clinical aspects with respect to the Natural History of NPC and barriers to a classical RPCT.

We know the natural history of NPC1. It is not pretty. It is a progressive, irreversible neurological disease that results in significant morbidity and death.

We have multiple sources of natural history data collected retrospectively and prospectively. Two examples are provided, but all the data shows the same thing:

- 1) NPC1 is a progressive neurological disease
- 2) The NPC1 phenotype is extremely heterogeneous
 - a. Age of onset
 - b. Individual progression rate
 - c. Individual signs/symptoms complex
- 3) Although clinical manifestations appear episodic - the neuropathology is continuous
- 4) Clinical progression occurs over years. A one year period has high probability of not being enough

The natural history data are not from controlled trials. However the various limitations of the different data sets does not mean that the data can not be used to accurately assess drug efficacy in a real life clinical setting.

These data can be statistically modeled to provide high confidence of clinical efficacy.

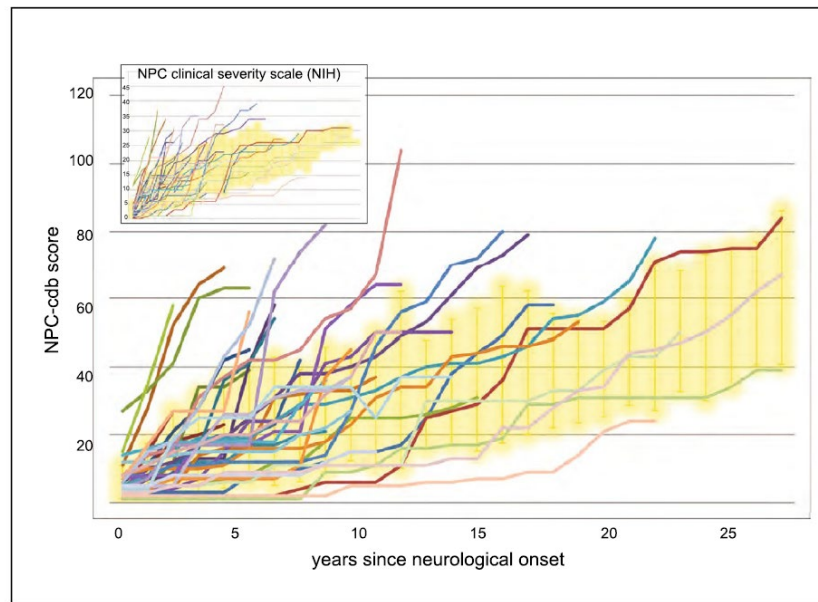
An example is shown on the right:

These data look at swallowing function in NPC1 patients treated or untreated off label with Miglustat. The data clearly show that Miglustat delays swallowing impairment as ascertained by both a qualitative clinical assessment and a quantitative measurement of aspiration on barium swallow. Dr. Patterson has published complimentary data showing increased life expectancy.

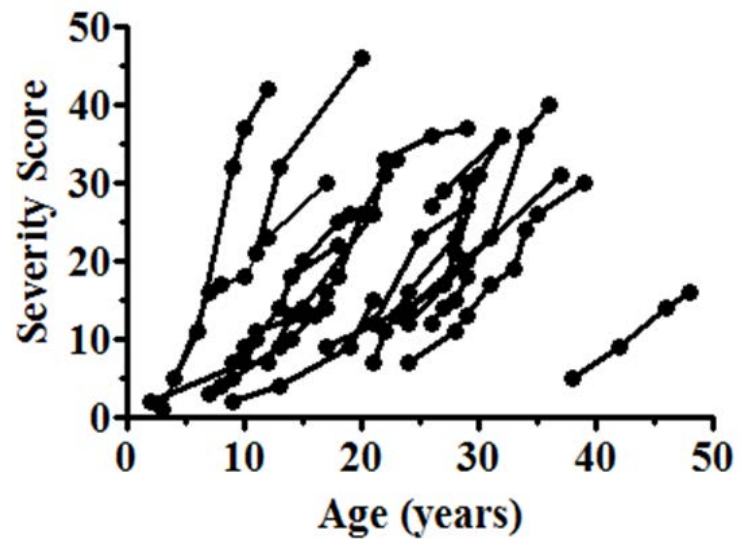
This slide also shows that to demonstrate clinical efficacy one needs to study these individual over years. The data on this slide took over a decade to obtain.

These are real life data. This is how the drug behaves in the clinic. This is what ultimately matters to patients.

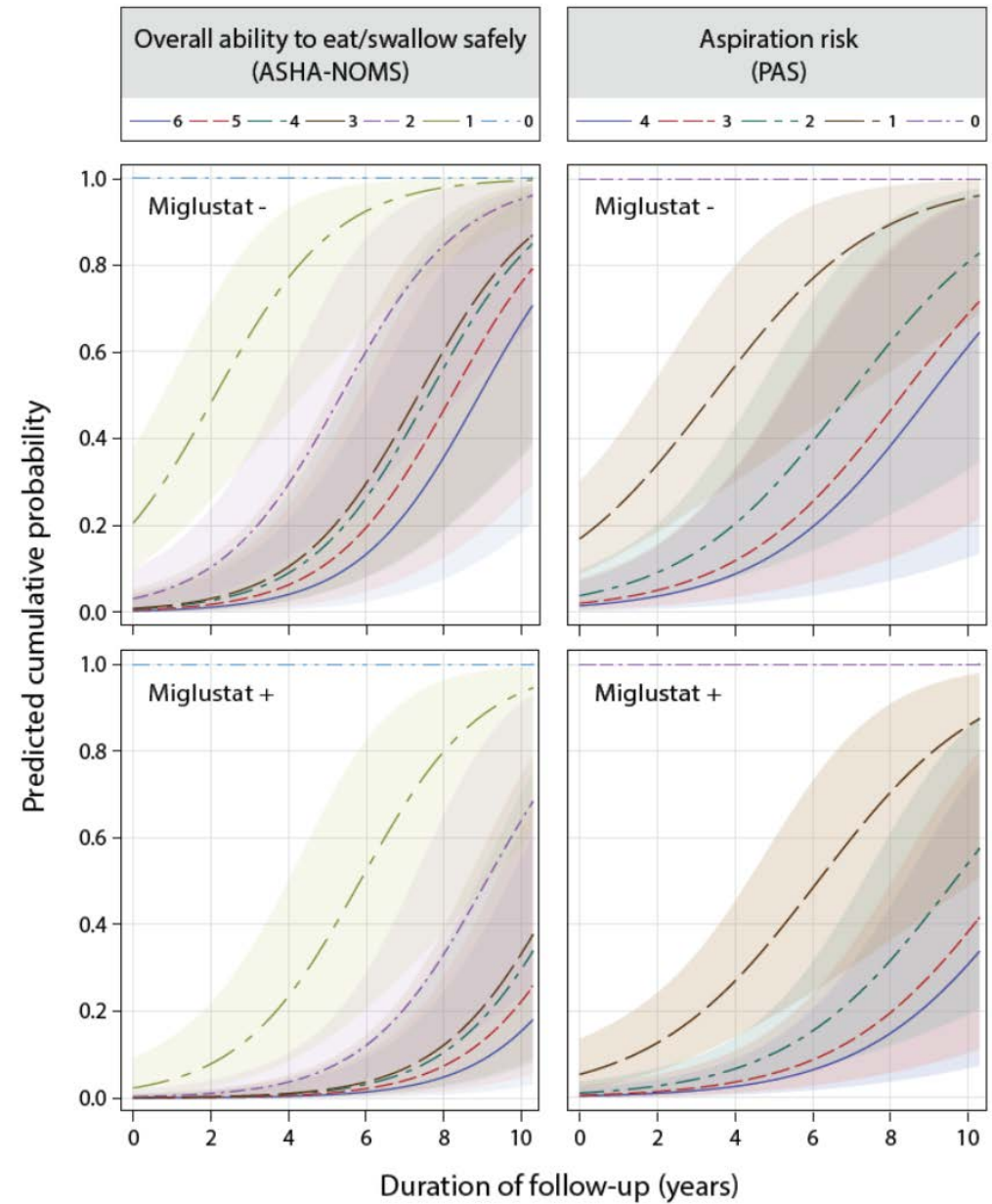




Stampfer et al. Orphanet Journal of Rare Diseases 2013, 8:35



Yanjanin et al. Am J. Med Genet Part B 2010, 153B:132-140



Solomon et al. JAMA Neurol, 2020, Online ahead of Print

▶▶ Access to Therapies

Dr. Elizabeth Berry-Kravis, RUSH University Medical Center

Dr. Elizabeth Berry-Kravis

RUSH University Medical Center



Treatments will work differently in different patients with NPC, making it hard to demonstrate outcomes in averaged groups, where the variability creates a mess. Most drugs will work better if started early in the disease course. Mildly affected patients, not eligible for traditional trials, when started on IT treatment through expanded access, have not progressed and even improved in some cases over 7 plus years, illustrating the need for long-term and within patient analyses to show true effects of any drug. Outcome expectations and new analysis models have to be individualized based on severity at treatment start to make sense – mildly affected patients may stabilize or even improve, severe patients may just slow progression at best. In fact, using these methods, a combined analysis of all treated patients and natural history showed a statistical treatment benefit for the IT treatment despite a failed RCT (first slide).

Very young children have more brain plasticity and represent a special group that if treated early may show dramatic responses, particularly contrasted against the usually more rapid disease course in untreated patients presenting at this age. As an example, patients who were started on IT treatment through expanded access before age 5, many early in the course of neurological symptoms, are shown in this graph which compares all 21 of these treated patients (top graph) to the early onset patients pulled out of the Vanier plot that shows the variability of disease course at all ages. Bars for each individual patient are plotted against age. Green represents the time of life before neuro symptoms, blue post-neuro symptoms alive, red post-neuro symptoms deceased in both graphs, purple treatment time in treated group. Most of these treated kids are alive, in contrast to the natural history kids. We have seen improvement in developmental trajectory, and ongoing development to the present in most cases, rather than the expected outcome of progressive loss of skills. Early IT treatment has made the difference between retaining the ability to walk, talk, and swallow – or not. Even those with moderate symptoms have stabilized, although patients with endstage disease at treatment start have not benefitted, including the two who didn't survive. I would argue that this cohort of children is getting to the age when we will be able to determine that they are doing better than natural history just based on the fact that they are not dying. Certainly 5 more years of treatment would answer the question of whether we have changed the course of disease in these children. (next slide)

This video of a 4 year old patient who was regressing before starting IT treatment going up a slide before and after treatment is an example of the remarkable difference in skills we can see in an already regressing young patient after just 8 months of treatment. (next slide)

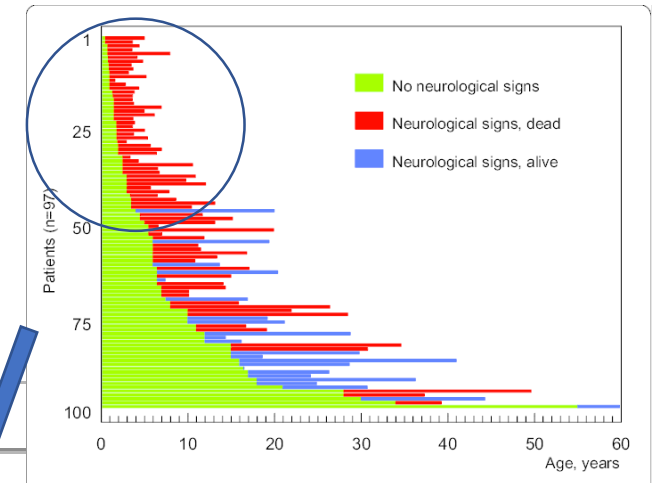
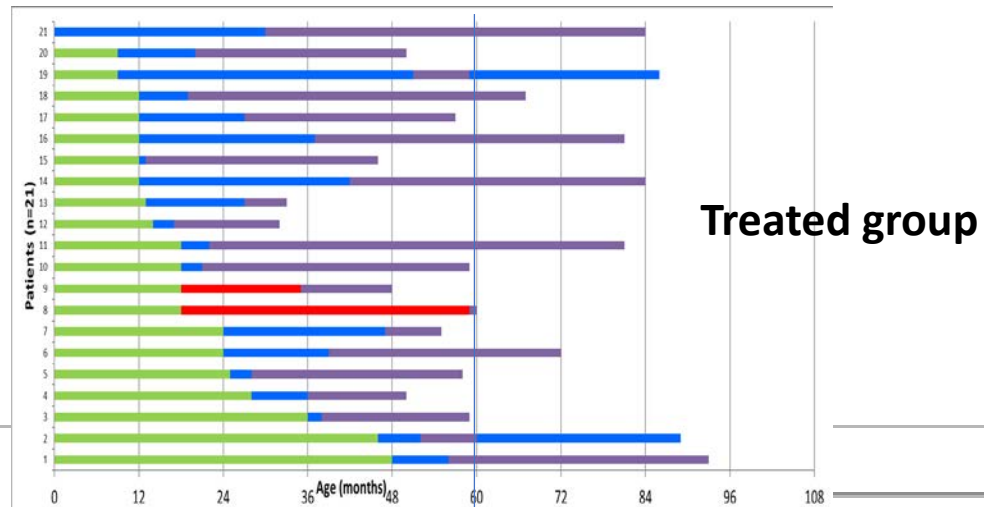
Dramatic examples of long-term benefit of IT treatment are seen in siblings. Here, the sibling on the right had disease onset at age 3 and at 6 years 10 mo had not been treated. You can see her gait issues but you can't see the speech, fine motor and swallowing problems. Her sister on the left, treated at 22 months when she had minimal neurological symptoms, functions normally after 5 years of treatment. (next slide)

In another pair of siblings – the untreated child at age 6 is wheelchair bound cannot talk and has a G-tube, his brother who started treatment at age 3 when he had early disease and no speech, can walk, now talk (although dysarthric), ride a bike, write and attend school on-line. This 3-5-year treatment outcome is clear, life-changing and very different from what is expected in early onset NPC.

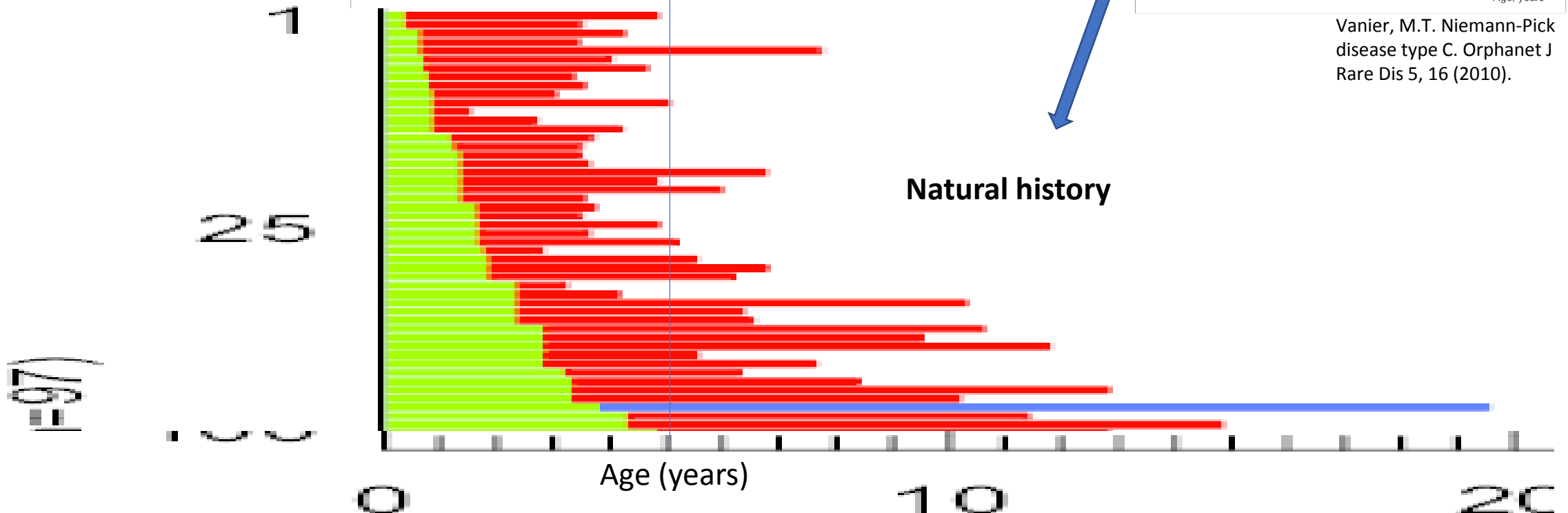
I currently have patients age 9-24 months whose development is stagnating or beginning to regress. For other patients with similar trajectories, treatment has made the difference between ongoing developmental progress and massive losses over the next years. These patients don't have time for new trials or development processes. It doesn't seem ethical to deny them or others access to a treatment because of a questionably feasible failed RCT that did not even address the young age group. If a drug is safe and shows potential signs of benefit, it is important to ensure long-term access in order to do the studies needed to demonstrate whether there is a long-term benefit and to offer all possible therapies to patients with a horrible fatal brain disease as early as possible. This could involve a program for conditional approval followed by removal of approval after 5-10 years if efficacy is not demonstrated based on natural history or within-patient comparators. Thank you for listening.

Trajectory of Children with NPC and Onset/Treatment Under Age 5

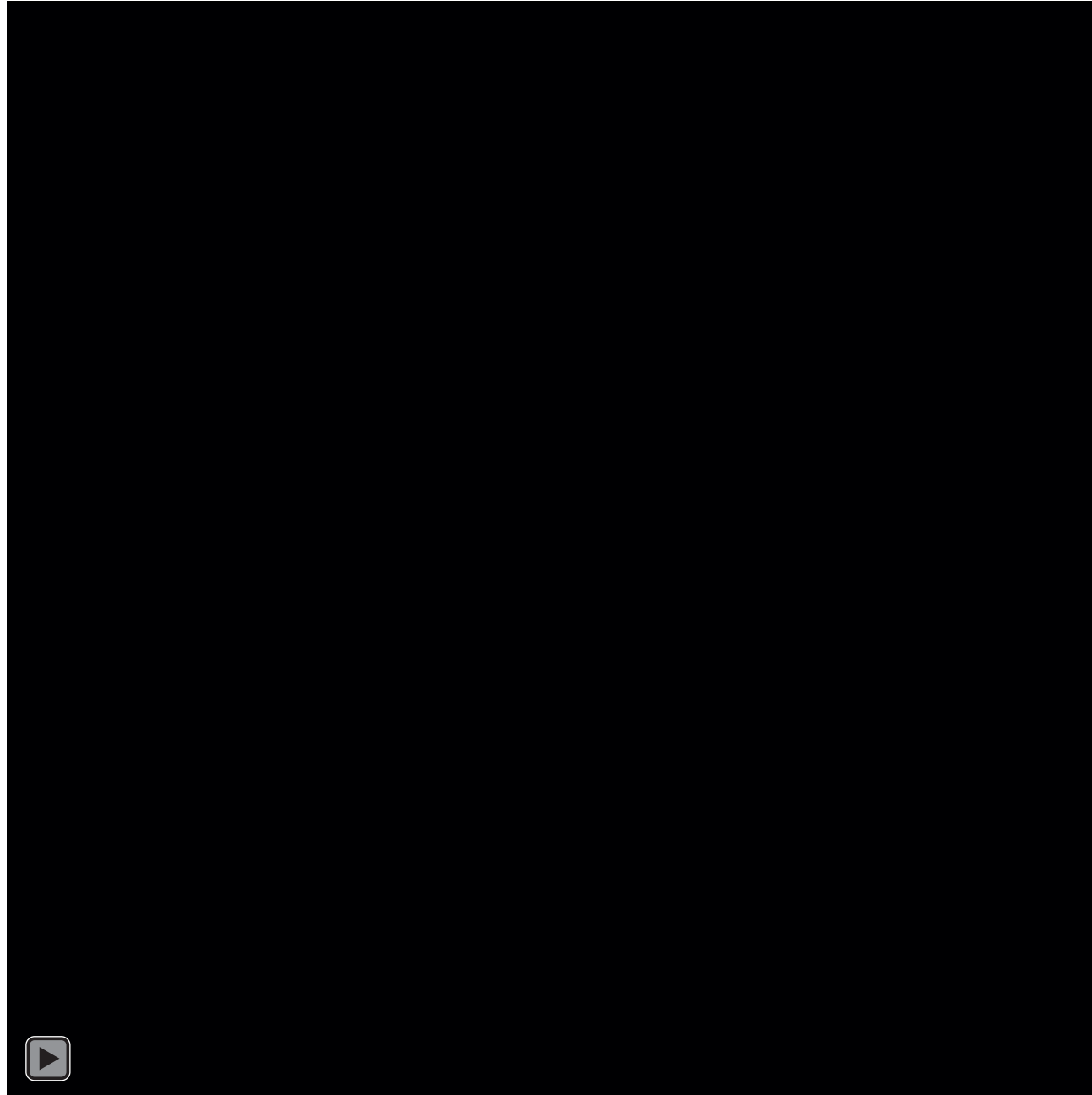
- No neurological signs
- Neurological signs, dead
- Neurological signs, alive
- Treated



Vanier, M.T. Niemann-Pick disease type C. Orphanet J Rare Dis 5, 16 (2010).



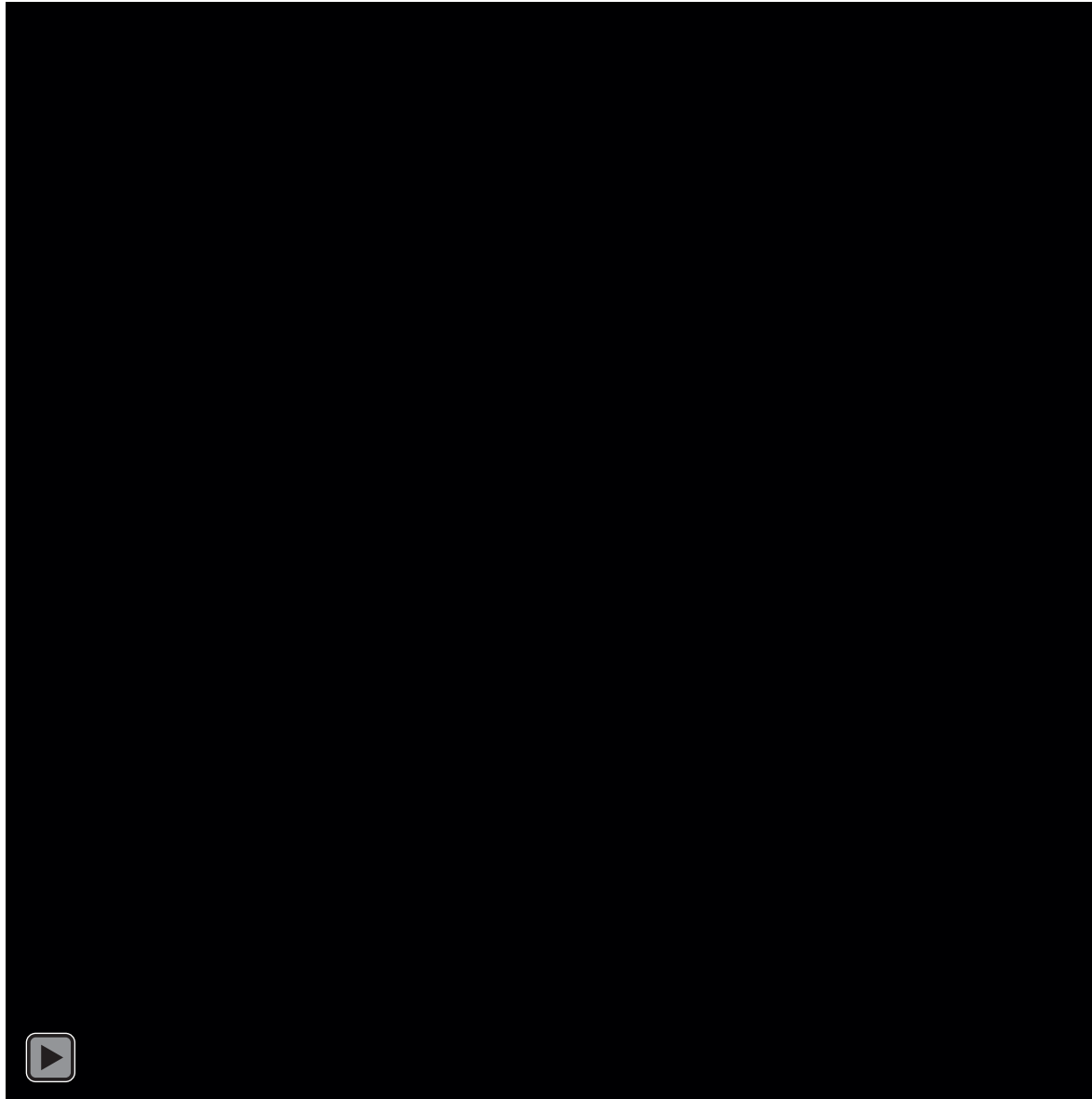
**3 months pre-
treatment
Age 3.7**



**8 months post-
treatment
Age 4.6**

**Untreated older
child age 6y 10m**

**Also swallow
problems, speech
dysarthria, fine
motor impairment,
cognitive
impairment**

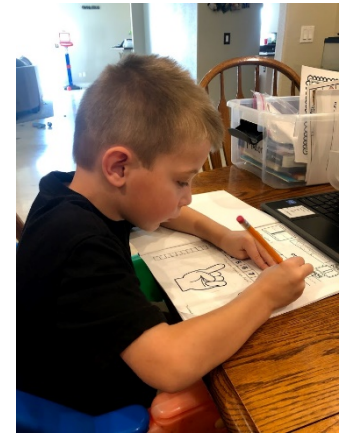
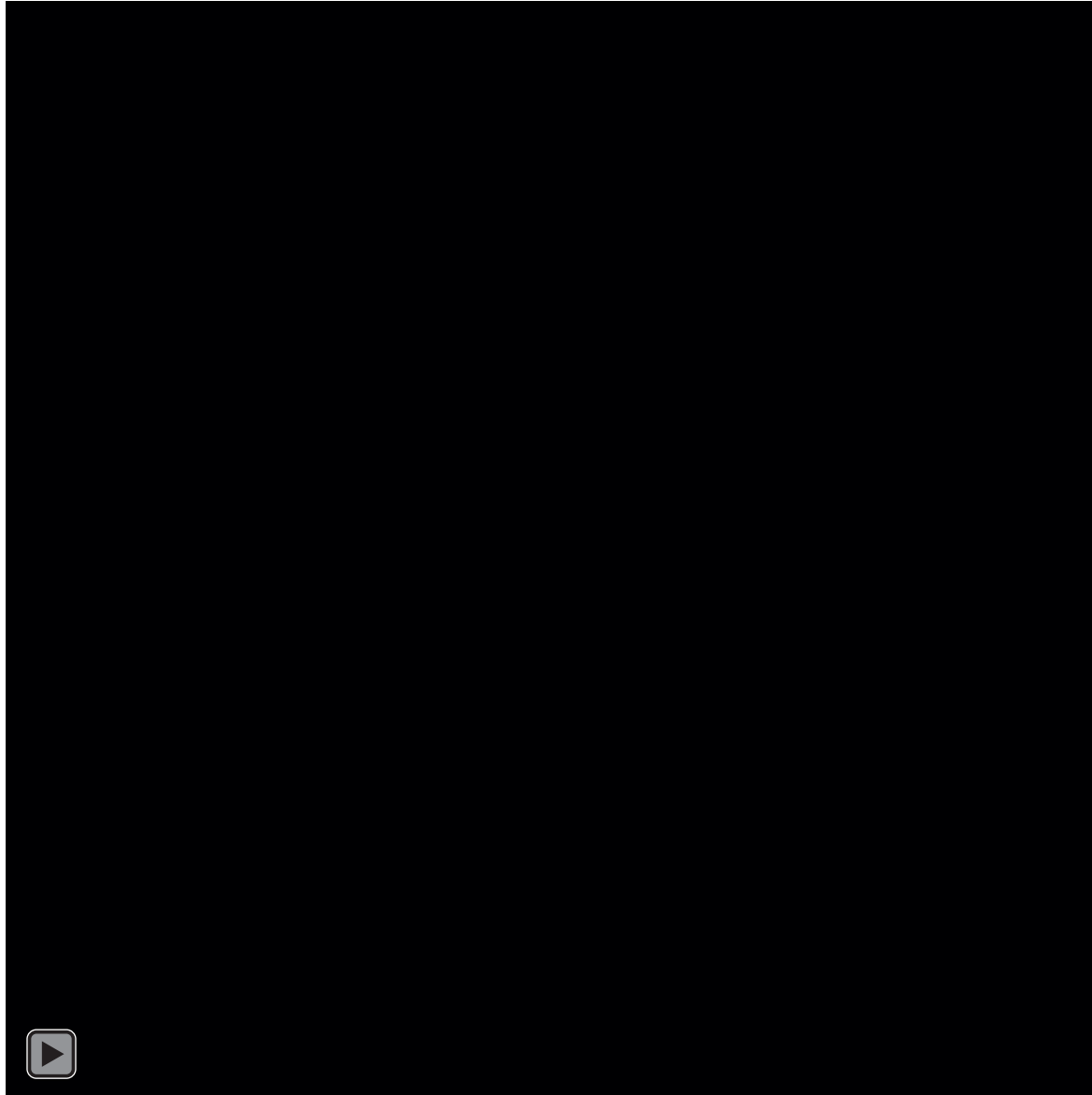


**Younger sister,
treated early at
age 2, on
treatment 5 years**

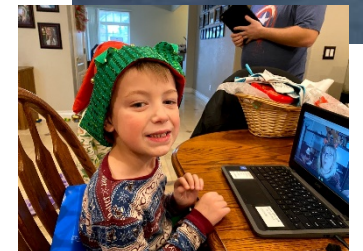
Functions normally



**Untreated sibling –
age 6**



**Treated sibling –
age 6, Started
treatment age 3**



▶▶ Patient Voices

Rebecca Spencer-White
Parent of Johnathan, NPC



Rebecca Spencer-White

Parent of Johnathan, NPC

Johnathan was born in 2006 and appeared to be a beautiful healthy baby. But within days, it was clear something was very wrong. He became septic, extremely jaundiced and had an enlarged liver and spleen. Over the course of the next several days, Johnathan was in complete liver failure and the doctors thought he would need a liver transplant.

Johnathan's liver and spleen remained unusually large and continued to grow for the next few years. Just before Johnathan's 4th birthday, we got a heartbreaking answer when he was diagnosed with Niemann-Pick Type C. **I still remember getting the phone call and screaming.** It was the worst news any family could ever hear.

By the time Johnathan turned 7, he had visible signs and symptoms of NPC like learning issues, swallowing problems, and balance issues. At that time, he had an opportunity to join a trial at the NIH for an investigational medicine. We had no idea what the benefits might be but we did know the alternative was death. At the time Johnathan was the youngest patient that was enrolled in the Phase 1 of the clinical trial.

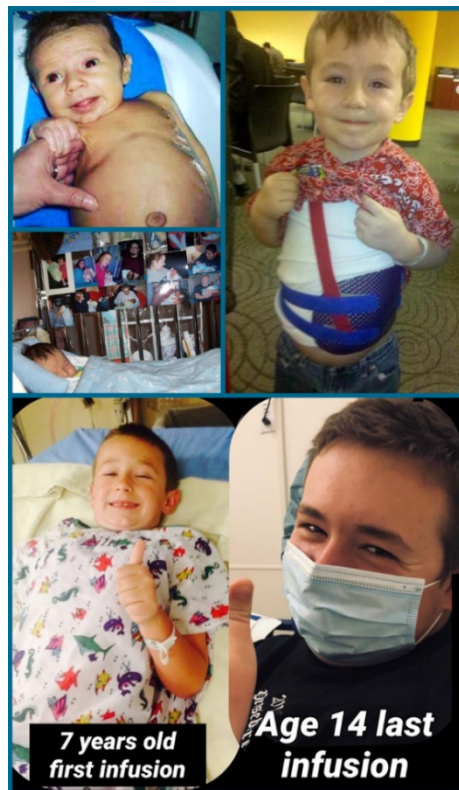
We were relieved when within just after a short amount of time in the trial, Johnathan no longer had the swallowing issues we had seen before and his other symptoms stabilized completely. We were so hopeful.

Over the course of the next 8 years while receiving this medication, we saw Johnathan retain most of his abilities and independence. He exceeded everyone's expectations and recently celebrated his 15th birthday. He has been able to experience the normal things of growing up – like crashing his go cart!

Devastatingly, on January 26th, 2021 after 8 years on the medication, Johnathan had his last treatment after a letter was received by our hospital from the pharmaceutical company that makes the medication. We were **devastated and terrified** of what this would mean for Johnathan. Within 4 weeks of Johnathan's last treatment, he developed swallowing issues again. Today, it is a struggle for him to drink liquids and he chokes at every meal. Also, his walking has regressed - he is now in aggressive braces to assist him in walking and his speech and stuttering has worsened. Without this medication, Johnathan's NPC is **progressing rapidly**. We feel helpless! Denying this medication to our NPC community is heartbreaking.

We have heard that the data did not show a benefit in our small community, **but that is not the reality that we know**. We really do feel in time, the science will show the benefit to this treatment. But we do not have time!

Thank you so much for giving me the opportunity to share Johnathan's story. **Time is running out for our families. Please help us find a way to save our children.**



▶▶ Patient Voices

Sara Peterka

Parent of Emma, NPC



Sara Peterka

Parent of Emma, NPC

Hello. Thank you so much for listening to us today.

My daughter Emma is two and a half and the absolute light of our lives. She is the sweetest, kindest, bravest little girl who lights up every room she enters and captures the heart of every person she meets, with her contagious smile and bright teal glasses.

We were devastated when she was diagnosed with Niemann-Pick Type C last September, after a significant decline over the summer. She had lost basic skills, such as moving across the room, feeding herself independently and using sign language to communicate. It was heartbreaking to watch. Upon diagnosis, we took Emma to see Dr. Patterson at the Mayo Clinic who recommended that we immediately start an intrathecal therapy. Emma had her first lumbar puncture the following week.

Within a month, her disease progression had stabilized. It felt like a lifeline in the darkest time. We started to feel **hope**. Just after Thanksgiving, Emma started picking up a fork again and bringing it to her mouth to feed herself. Not even six months in, she has gained so much strength that she went from not being able to sit up on her own without tipping over to sitting sturdily and upright without support. This disease only takes away, it doesn't give back. And yet we're witnessing Emma regain skills and strength; she's becoming more verbal after sadly losing the ability to say "mama;" she's showing an interest and curiosity in things around her, something that had faded many months ago. She is gaining and developing when she should be losing and deteriorating.

As the benefits of this drug became more apparent week by week, we received the unimaginable news that we were going to lose access in October. We have witnessed the impact of this intervention and the power of this drug. It has resulted in dramatic change and developmental gains for Emma. We're terrified to lose access because that means we will begin to lose Emma - again. Please don't let that happen. Please find a solution that keeps access to this drug for the NPC community. If Emma had been diagnosed just a couple months later, she would've been locked out of access to this therapy, and that thought haunts me every day.



▶▶ Patient Voices



Denise Miller
Parent of Woodrow, NPC

Denise Miller

Parent of Woodrow, NPC

Hi my name is Denise Miller and I am the proud mama of Woodrow Miller who is 20 months old. Woodrow is our only child and the light in our lives. Woodrow is a very happy child that has a smile and giggle that lights up the room.

On October 3, 2019 our walls caved in and we knew it was possible for the heart to break because ours shattered. Woodrow was born premature with extreme liver dysfunction which led to the diagnosis of NPC at 3 months of age. Woodrow participated in the neonate trial through WashU with successful results. The trial ended in August 2020. In October of 2020 Woodrow's development began to stagnate. Since he was a preemie, we decided, with our doctor, to give him a few more months to develop and then reassess the need for IT. However, at the end of January, Woodrow had clearly fallen off the curve and the time was NOW to start him on IT. Except, now he is being denied access.



Woodrow is now 20 months old and has had NO developmental gains in over 6 months and is beginning to show signs of regression. He is at the level of a 12-month-old. He has uncoordinated gross and fine motor movements and a lack of balance. He cannot sit on the ground without swaying back and forth. He does not walk and without treatment he never will. He speaks 1-2 words and as of recently will go days without saying words at all. He is becoming more and more withdrawn and solemn and non-interactive with each passing day. With each passing day I am losing a piece of Woodrow we will never get back.

I have directly requested that pharma grant access. Others are receiving access, but there are many families denied access, like myself - I am being told no! **No parent should have to bury their child when there is an effective treatment available**, that just simply cannot be accessed.

Woodrow does not have a month, two months, or 6 months for something to be done. He needs intervention NOW and if you are listening to me speak you have the power to change the outcome of Woodrow's life. Soon it will be too late for Woodrow, statistically he will have lost every skill he has, enter a vegetative state, until he dies before seeing his 3rd birthday. Please take seriously the decisions being made. Please give Woodrow the access to treatment he deserves. Please do not let Woodrow continue to wither away and with each passing day watch a little bit of his sparkle leave his precious little body.

▶▶ NNPDF & Niemann-Pick Community Recommendations

1. Use our community as a model for novel clinical trial design in rare disease
2. Consider conditional approvals when a clinical trial confirms safety and real-life data suggests benefit
3. We unequivocally stand behind ALL our clinical programs
4. Help us ensure access to miglustat
5. Partner with our community to find a path forward for adrabetadex

Closing Statement

Dr. Justin Hopkin, NNPdF Board Chair

Before I close, I want to thank the FDA for this opportunity to share our voice. I want to thank our clinicians and researchers for dedicating their careers to finding a cure for NP-disease, and I want to thank all our patient speakers for sharing their personal stories today. I now have 5 requests to present on behalf of the community.



1. We reviewed the pitfalls of traditional clinical trial design in an ultra-rare disease where very few patients are now drug-naïve and the irreversible loss of function related to prolonged placebo is an unacceptable risk. Partner with us to design novel clinical trials that utilize natural history and within-person analysis to limit the role of placebo.
2. It is very difficult to conduct a successful traditional clinical trial in a heterogeneous disease that has variable progression. When clinical trial data demonstrates safety of a drug but may not reach the pre-determined endpoints, please accept real life data that may suggest a drug's effective over a longer period of time or in subgroups of patients. In these situations, we request conditional approval to provide drug access with ongoing monitoring for safety and efficacy to generate the long-term outcomes needed to truly understand the drug's impact on the disease.
3. Unfortunately, there are no cures in the pipeline for NP disease, so we will need multiple effective therapies approved to address different aspects of Niemann-Pick Disease and render it a chronic disease. We are fortunate to have four safe agents in the later stages of clinical development that have all demonstrated efficacy in clinical trials. As a community, we emphasize our wholehearted support for all our clinical programs and the benefits we have experienced with each agent. While we didn't have time to share impactful patient experience with each agent today, we can and will in future sessions. Our ultimate goal is access to FDA approved therapies for NP-C and ASMD and we implore your ongoing support of these clinical programs.
4. Our community has extensive experience with off label miglustat to treat NP-C. With more recent evidence emerging which strongly suggests a benefit in clinically relevant long-term outcomes, we want to work with the FDA to ensure that access is maintained for all patients and hope to partner with you to create an expeditious route for approval of miglustat in NP-C.
5. You heard from several families today about their experience with adrabetadex, a drug whose future is uncertain and the need for intervention from us is immediate. We are strongly advocating for continued EAP access and request FDA guidance on what we can do to move the program forward. We would like to schedule a meeting in the very near future specifically for our NP-C families to share their positive experience with adrabetadex and work with you to create a new path forward.

We thank you for your time and welcome your questions.

▶▶ Summary

Dr. Hylton Joffe, Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine

» Closing Remarks

Dr. Patrizia Cavazzoni, Acting Director, Center for Drug Evaluation and Research;
Deputy Center Director for Operations, Center for Drug Evaluation and Research
(CDER)