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

VIRTUAL PUBLIC WORKSHOP

January 24-25, 2022

FAMILY STATEMENTS

Debbie Kaflowitz

NPC Legacy Parent

I would also like to thank everyone, those who have given their time and energy behind the scenes and those who are sharing their ideas on Zoom.

I live in New Providence, New Jersey, with my husband Steve. Sadly, we lost our only child, Rachael, on October 25, 2018. Rachael's story is different from the others because not only did she have adolescent/adult onset, but she also never had treatment Rachael was diagnosed with NPC at age 26. My first conference was a year after that, and they were just showing positive effects with cats. By the time treatments were accessible to Rachael, it was too late because the decline was too great.

Adult onset has some different symptoms and challenges than other forms of NPC. Not worse, just different. As Barb said yesterday, patients with adult onset often begin with psychiatric problems. Rachael's final psychiatric diagnosis was schizoaffective. Her first breakdown was her junior year of HS and over the next 12 years, she was in and out of hospitals with doctors trying everything to get her stable, different medications, different doses, different combinations and then shaking their heads and sending her home where we were her caregivers, and she couldn't be left alone for even a minute. She eventually did get stable enough to function with many breakthrough episodes.

During that time Rachael also experienced cognitive decline. At first it was noticeable in school. However, then it took a more serious turn. She started losing lost her short-term memory. I asked the doctor if people Rachael's age could have Alzheimer's because she and my father, who had Alzheimer's, looked exactly the same cognitively. She also lost her ability to reason and understand cause and effect. She was in a wheelchair and if she saw something in the room she wanted, she would try to get up from her wheelchair, which would usually mean a trip to the emergency room. The welcomed her by name there.

Although the progression in adult onset is expected to happen slowly, but things can go downhill quickly. In a period of about 5 months, she went from walking fine to holding onto us to a walker to confined to a wheelchair.

With hand tremors she went from making her own jewelry to not having any control over her hands at all. She couldn't even control her hands enough to pet our dog.

Regardless of the age, when progression is happening to you or your loved one, it feels like every time you turn around something else has been lost.

One of the most devastating parts of adult onset is an emotional component. For the young adults it's knowing that your peers are moving forward, and you are moving backwards. For older adults, it's having a life and then knowing that it's slipping away. I know people with NPC who were captains of HS sports teams, doing fine in college or a job, living on their own, starting their own family, when all of a sudden, out of the blue, life starts falling apart. Before Rachael got sick, she danced in ballet recitals, baby-sat and was a fabulous camp counselor because of her talent with children. She had her driver's license. Rachael planned

on going to college, having a family, and becoming a teacher, but each dream disappeared little by little.

Rachael couldn't do anything she planned, yet in the beginning, she was much more socially aware and able to engage in more activities than the people at the day programs we found. I call this time, having one foot in the regular world, one foot in the disabled world, and feeling like you don't fit anywhere.

One of the most devastating things for us was when Rachael would ask questions that showed she was still aware of her decline, like "What am I going to do about me?" or "Who is going to marry me like this?" and the worst I remember "I used to have friends when I as a person. "

Rachael was doing well at the end of August of 2018. When I say well, I'm talking about NPC standards. She couldn't do anything for herself, the list of foods she could eat had become very small, and she was confined to a wheelchair, but she enjoyed the NNPDF conference and our short trip to the Jersey Shore. Two weeks later, Rachael came down with the flu and entered the hospital on Sept 8th where she started fighting for life. Then she developed pneumonia. After a two-month fight, Rachael passed away at age 33 on October 25th.

Last Words

First, thank you, Dr. McClennen, and all the other moderators who made the caregivers comfortable so we could share information about a very personal and difficult part of our lives.

This has been a great meeting of the minds. Lots of food for thought. But on behalf of the caregivers on the panel and anyone listening who is personally affected by this disease, we have to remember that there are real people behind this conversation. There are babies and the oldest person I know personally is in her 60's. Right now, there are parents sitting by their son's bedside. He's a young adult, who seems to be following Rachael's path. And there will be dozens behind him. We can give patients longer and better lives. We need to continue talking but also start acting, so no other people go through what my family did.

Alec Koujaian

NPC Affected Individual

Hello. My name is Alec Koujaian and I have Niemann Pick Type C. I was diagnosed in January 2012 when I was 14 years old. I have been getting treatment since December 2013 via Dr. Kravis's expanded access program. That is over 8 years of treatments. I just had my 201st treatment.

I have participated in several community sessions with the FDA. In the last session, I kept hearing that the FDA was not sure the benefits were real. I am here to tell you that the benefits are real, and the treatments are safe. Why else would I have 201 treatments if I didn't think so? Why would families from India, Russia China and the Netherlands move to the US so that their loved ones can be treated if they didn't think the benefit were real? Why would doctors from all over the world provide treatments if they were not convinced of the benefits?

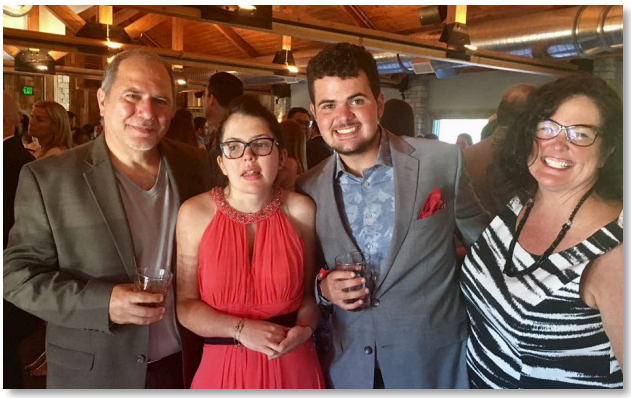
It all comes down to that I live a normal life. I graduated from college with an Associate Degree in Fire Science. I work over 30 hours a week and drive a car. I do chores around the house and play with my dog Luci. I enjoy going out with my friends to eat, go to movies, concerts and playing sports. Life is good

In the last session I heard the FDA is concerned about the NPC Severity Scale. I am really trying to understand that. It was good enough before the trials, but now it's not? I don't get it. I learned that the FDA is denying access for some patients to get the same treatment that is helping me and also denying other therapies that will help me because the NPC Severity scale needs 'minor tweaks. That is fine. I am sure all the experts involved will work to improve the scale, but don't take our treatments away while it is being tweaked. I need them to continue to enjoy my life. The NPC community cannot live in this constant state of worrying if these treatments, that many have been on for decades, are no longer available. This would be a death sentence to many.

I am happy to see so many new doctors and experts involved with the Duke Margolis session over these 2 days. I invite anyone of you to spend time with me and Dr. Kravis during a treatment. Hopefully you can learn from us while we work with you towards the future. Thank You.

Harry Koujaian

NPC Parent & Legacy Parent



My name is Harry Koujaian. I am the father of Alec who is 23 years old and who you will hear from shortly, and Hayley, who passed away from complications from NPC on April 3rd 2020 at the age of 20.

I would like to thank the Duke-Margolis team for including NPC parents, patients and industry experts in these sessions. I would also like to thank the doctors you heard from yesterday and which you will hear from today who have been treating our kids with NPC for decades. They are the expert in this field and glad you are hearing what they have to say.

I just want to make sure that everyone listening to these sessions understand 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. And to put this in prospective, think of NPC as the having the combination of the short-term memory loss of someone with Alzheimer's, the tremors of someone with Parkinson's and the systematic decline of someone with ALS. Fortunately, there are treatments available that NPC patients are on that slow down or stabilize disease progression. These treatments work. My son is an example of this. Unfortunately, these treatments are being subjected to constant attack. I always wonder how much these decision makers really know and understand NPC specially when the opinions of our doctors, clinicians and researchers who have dedicated so much of their life in the front-line helping NPC families, are questioned and ignored. It is disheartening and frustrating.

I would like to share some of my concerns with the panel and the audience.

NPC is always fatal. The urgency is now. Here are some numbers to think about, 15% of children have passed away from NPC by age 5, 31% by age 9 and 55% by age 15. Time is not on our side.

I am happy to see that the topic of Digital Health Tools is being discussed here. It will certainly add to the arsenal of assessments that are currently being collected. I just want to make sure that any data collected over many years from various sources such as the Natural History and Expanded Access program are not ignored. When you have a rare disease, these types of data is irreplaceable.

You have heard from Dr Porter and many others that about all the work that was already done to collect data and some of the solid endpoints we already have such as with Miglustat. We should build on this.

I heard that the FDA has flexibly in serious rare diseases such as NPC which is great. However, I would argue in our case, that just the opposite has occurred from questioning the same endpoints that were accepted in the initial trial design and later rejected, to putting clinical holds on the Expanded Access program such that less and less of our NPC kids are able to get treatments. To paraphrase the famous saying "Show me the money" from the movie Jerry Maguire, I would like to say "Show me the flexibility"

We will work with anyone and everyone on building new tools to measure disease progression, but we must work with the data that we have now and dive into it so we can have a path for approval for these therapies that are saving our children. Maybe this should be the topic for our next Duke-Margolis meeting and hopefully very soon.

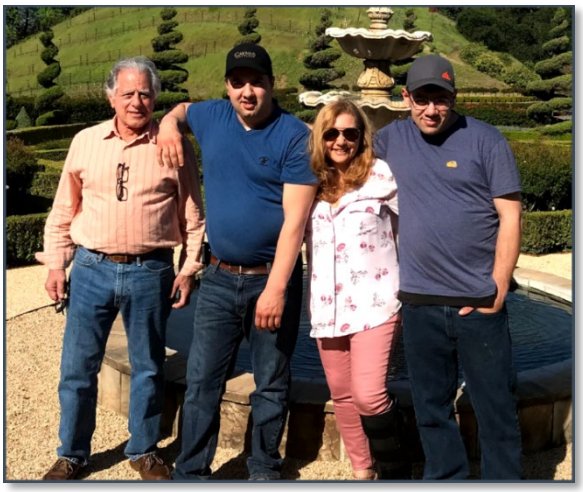
The FDA must listen to the voice of the patient. Telling the NPC community in front of us that they hear us and then repeatedly tell us in other settings that there are no benefits and that there are safety concerns goes against what the families and the patients have been telling the FDA at every occasion – that yes, the benefits are real and the safety concerns such as hearing loss, are well understood and accepted by the NPC community. As we repeatedly say, “I rather have a deaf kid than a dead kid”.

Lastly my main concern is that while it is great to have meetings such as this to try to develop the additional endpoint and design the perfect trial for an ultra-rare disease such as NPC, our current treatments will no longer be available to us and my son and many others, who have benefited from these treatments for years, will start their decline. That is my main concern. But be assured that we will never give up.

Thank You

Barbara Lazarus

NPC Parent



I have 2 sons with adult-onset NPC diagnosed just over 4 years ago. Daniel is 35 and David is 32; their initial symptoms were psychiatric in nature which led to many lost years of misdiagnosis and opportunities for treatment. They are currently participating in 2 different trials, Daniel in IV Cyclodextrin and David in the Arimoclomol EAP; to be clear we feel that both treatments have allowed them to maintain their separate levels of independence and that their progression has not been what we were led to expect.

I am also a speech and language pathologist who has worked in both the rehabilitation and educational settings, working mainly with the early pediatric population

Both of my sons have dysphagia presenting at different levels of impairment with different profiles, one oral phase difficulties and the other primarily pharyngeal phase but both remain independent eaters.

After diagnosis, their swallows were first assessed using the swallow domain of the CSS. From both a caregiver and professional viewpoint, I have always felt that the scale has correlated accurately with what I was observing in both of them. They have subsequently had baseline and follow-up Modified Barium Swallow evaluations which have consistently supported the levels seen on the CSS.

While the MBS and similar instruments capture the physical parameters of what is happening at that moment in time and informs diagnosis and treatment plans, it does not capture the variables that affect swallow on a real-life daily basis and that is why I feel it is imperative to include patient/caregiver observations and reporting in whatever protocols are developed. As a clinician and a parent, I feel strongly one can never replace what is observed on a day-to-day basis.

I also feel in the case of NPC, that the extensive body of information we have already obtained through the NIH study, current and past trials, in addition to other sources is vital in developing future protocols as this is information that cannot be duplicated given the limited number of patients identified with this disease and the urgency to provide treatments that have proven efficacy and effectiveness in slowing the progression.

Phil Marella

NPC Parent & Legacy Parent

I'd like to start out by emphasizing that NPC is a fatal disease. It is taking our children piece by piece every day, stealing neurons every day.

My wife Andrea and I live in Connecticut. 2 of our 4 children were diagnosed with NPC, Dana at age 8 in 2002 and Andrew was almost 5 in 2004.

When Dana was diagnosed, we were told she would live to only 13 or 14. That was the story of NPC for too many families before our experimental treatments. IT WAS SAID EARLIER THAT NPC IS A SLOWLY PROGRESSING DISEASE. I'D LIKE TO REPSECTFULLY POINT OUT THAT 5 YEARS LEFT WITH YOUR CHILD IS NOT A SLOWLY PROGRESSING DISEASE.

The diagnosis is a horrific reality that immediately devastates a family….everything in your life is turned upside down. When Andrew was diagnosed with NPC 2 years after Dana, having a second child with no available treatments makes you feel like you'll never take another breath. By 9, Dana couldn't walk without a special supportive walker. By 11 she was in a wheelchair, by 12 she had a feeding tube and was soon non-verbal.

Continuing to decline, Dana required 24/7 care by age 16, had numerous pneumonias and eventually a trach and a respirator. She was on Miglustat from age 11 and died in 2013 at 19 years old, but we had 5 or 6 additional, wonderful years with HER than we originally expected because of her medication.

Andrew on the other hand is now 22, still conversant, joking, laughing, feeding himself and able to walk with some assistance. He works part-time as an usher in a movie theater. He's been on Miglustat for almost 18 years starting at age 5 and on Cyclodextrin for 8 years. It's a real blessing, but we know that NPC is still stealing neurons EVERY DAY, just more slowly WITH THE intervention.

The saddest thing is that he saw his sister die, and he feels NPC will take him as well. It doesn't really matter how often we tell him we will stop this disease. And we need everyone's help, here and beyond to make that happen FOR ANDREW and the other patients.

QUESTION POINTS:

We've talked about this being a scientific meeting and we want to stick to the science. But the science of the severity scale really hasn't changed in 10 years. What has changed is the staffing at the FDA.

At the 2013 NNPDF Family Conference, this community told the FDA that we would accept deafness over death. And the FDA heard us.

When the first patient suffered some marginal hearing loss in 2015, we all held our breath, but the FDA said we heard you…continue on.

Now we're told minimal hearing loss is too great of a risk.

In 2016 the FDA said, in my presence, that the composite endpoints, our 5-point domain scale, had been DEMONSTRATED to be meaningful and valid.

Now we're told it's not good enough.

So mid-stream we're faced with changing policy, NOT changing science and no one can succeed in that environment, YOU CAN'T SCORE when the GOAL LINE keeps moving.

Sara McGlocklin

NPC Parent

Hi, my name is Sara McGlocklin, I'm mom to a feisty 6 year old daughter, Marian, who has NPC.

Marian was diagnosed with NPC at 18 months old - she had global developmental delays. She couldn't walk, or even stand on her own, wasn't gaining weight, and had just started and then stopped waving bye bye, regression hadn't begun yet but signs where it was coming soon.

At diagnosis, we learned one of Marian's NPC proteins is minimally functional and the other completely nonfunctioning. There were no available clinical trials for her. Without treatment, her symptoms and natural history data tells us she would probably have died or lost most of her abilities by age 5.

We quickly began flying from Los Angeles to Chicago every other week to begin an experimental medicine through expanded access that had been studied for almost a decade. At the time Marian was the youngest in the world to do so. Marian religiously participated in days of testing and data collection every 6 months. Because of early intervention, after a handful of treatments, she took her first steps and pushed herself up from the ground, beaming and said "ta-da."

Almost five years later, Marian is not only blowing us away with her progress, she is blowing the disease's natural history away as well. Last summer she jumped for the first time ever and recently won an academic award after getting a 100% on her math test and is still gaining skills in every area. Some areas of change for her were swift and immediate and others have been slow but steady.

This disease is highly variable, but so are all diseases. And even though it presents differently, there are undeniable consistencies: NPC is always progressive, it is neurodegenerative and patients always decline in at least one, often multiple, key areas. And what we've seen with Marian is something that's not seen in natural history, patients don't spontaneously improve where they are suddenly speaking and jumping for five consecutive years - ever. Similarly, the disease doesn't spontaneously relent and stabilize once patients are rapidly losing skills.

I ask you to not look at this disease in silos but rather as the full picture. Testing results are snapshots. It's a reflection of what our children and adults can do on one of their hardest days, and I guarantee you they can do even more at home. So when these numbers show a slowing or stalling of disease progression for that patient - this is absolutely phenomenal and needs to be recognized as such.

We are happy as families to give data, but we cannot sacrifice any more lives and abilities to placebos as a control when we already have three placebo-controlled studies and a natural history study. We want to do the testing, to help our own understanding and advance science, but what destroys us is when it's dismissed as a variance or not considered "good enough".

When we see a patient doing something that defies natural history, that's an intervention that's working.

There are a few understandings that I hope we will walk away with today:

First, that early intervention matters and once there are early symptoms patients deserve access to treatment and this is urgent,

Second, reversing the effects of NPC is not realistic in the vast majority of circumstances. Rather, slowing progression in any area is a massive success; and

Third, the biggest risk NPC patients face is losing access to medications that are slowing disease progression and being denied the opportunity of combination therapy when there are multiple experimental medicines patients, and their doctors find beneficial but none of them are approved.

We must use our existing scientific and medical knowledge and build upon what we already have. We cannot sacrifice another generation of patients in pursuit of perfect data. This generation of NPC patient's lives are hanging in the balance.

From one parent to the many many many doctors and experts here today, thank you for being here and for your collaboration to help our families.