National Tay-Sachs & Allied Diseases Association

Canavan Foundation | Cure Canavan LLC

CANAVAN DISEASE

FDA Listening Session

In attendance:

Larry Bauer, Hyman, Phelps, & McNamara
Canavan Foundation
Cure Canavan LLC
NTSAD Staff
Families Affected by Canavan Disease

Office of the Commissioner (OC) – 3 Offices

- OC/OCPP/PAS – Office of Clinical Policy and Programs/Patient Affairs Staff (organizer)
- OC/OCPP/OOPD – Office of Clinical Policy and Programs/Office of Orphan Products Development
- OC/OCPP/OPT – Office of Clinical Policy and Programs/Office of Pediatric Therapeutics

Center for Biologics Evaluation and Research (CBER) – 5 Offices/Divisions

- CBER/OCBQ/DIS/PSB – Office of Compliance and Biologics Quality/Division of Inspections and Surveillance/ Program Surveillance Branch
- CBER/OCD – Office of the Center Director
- CBER/OCD/PS - Office of the Center Director/Policy Staff
- CBER/OTP/OCE/DCEGM/GMB1 – Office of Therapeutic Products/Office of Clinical Evaluation/Division of Clinical Evaluation General Medicine/General Medicine Branch 1
- CBER/OTP/OCE/DCEGM/GMB3 – Office of Therapeutic Products/Office of Clinical Evaluation/Division of Clinical Evaluation General Medicine/General Medicine Branch 3

Center for Drug Evaluation and Research (CDER) – 6 Offices/Divisions

- CDER/OND/ODES/DCOA - Office of New Drugs/Office of Drug Evaluation Science/Division of Clinical Outcome Assessment
- CDER/OND/ON – Office of New Drugs/Office of Neuroscience
- CDER/OND/ON/DNI - Office of New Drugs/Office of Neuroscience/Division of Neuroscience 1
- CDER/OND/ORDPURM/DPMH - Office of New Drugs/Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine/Division of Pediatrics and Maternal Health
- CDER/OND/ORDPURM/DRDMG - Office of New Drugs/Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine/Division of Rare Diseases and Medical Genetics
- CDER/OTS/OB/DBI - Office of Translational Sciences/Office of Biostatistics/Division of Biometrics 1

Center for Devices and Radiological Health (CDRH) - 4 Offices/Divisions

- CDRH/OPEQ/OHTIII - Office of Product Evaluation and Quality/Office of Health Technology III
- CDRH/OPEQ/OHTIII/DHTIIIA - Office of Product Evaluation and Quality/Office of Health Technology III/ Division of Health Technology III A
- CDRH/OPEQ/OHTIII/DHTIIIB - Office of Product Evaluation and Quality/Office of Health Technology III/ Division of Health Technology III B
- CDRH/OPEQ/OHTIII/DHTIIIC - Office of Product Evaluation and Quality/Office of Health Technology III/ Division of Health Technology III C

Objective

To provide an understanding of Canavan disease, an ultra-rare and autosomal recessive disease, including:

- The severity and impact of the progressive neurodegenerative symptoms,
- The impact the disease has on a family, and ultimately see the hope that potential treatments can bring to families today and in the future, and
- Our preferences that the selection of endpoints represent outcomes that are important to patients.

Kathleen Flynn, CEO, NTSAD (National Tay-Sachs & Allied Diseases Association)

Ms. Flynn introduced the session, the organizations involved in its planning, and a review of the meeting agenda, topics, and goals.

Although there are several individual families and organizations that advocate for Canavan disease daily, today's Listening Session is a collaborative advocacy effort that includes representation from the following three: the Canavan Foundation, Cure Canavan Fund, and NTSAD. On behalf of our organizations' leadership, advisors, dedicated staff members, and most importantly – the families we serve every day – we thank you for the opportunity to meet with you.

The Canavan Foundation is dedicated to educating at-risk populations about Canavan disease and other genetic diseases and the reproductive options available to carrier couples. The Foundation was launched in 1992, when Orren's daughter was diagnosed with Canavan disease. They did not want other families to experience loving and losing a child to Canavan. The Foundation encourages preconception genetic carrier screening and supports research towards treatments and a cure for Canavan disease.

Cure Canavan Fund was started in 2019 by two courageous parents from Brooklyn, New York, to support a fundraising crusade to help their children who have Canavan disease.

Founded in 1957, National Tay-Sachs & Allied Diseases Association (NTSAD) leads the worldwide fight to treat and cure Tay-Sachs, Canavan, GM1 - Gangliosidosis, and Sandhoff diseases by driving research, forging collaboration, and fostering community. The three pillars of NTSAD's focus are family services and support, funding research, and advocacy. With an experienced staff of seven professionals, including a dedicated Family Services Team of two, supporting families is the center of everything NTSAD does.

Before we hear from our first presenter, I extend our thanks to the members of the FDA who are joining us today. We appreciate your time and interest in learning about Canavan disease. And, thanks to the FDA Patient Affairs team who met with us in preparation for this session.

Publicly recounting their rare disease diagnoses and journeys is not easy, but the family members who are present today are deeply committed to advancing research and personally advocating for their children as well as for many families like theirs who cannot be here with us and speak to you today. They are also representing a multitude of families who lost their beloved children to this rare disease. Thank you to Orren Alperstein who will provide an overview of Canavan and share her personal family experience. And a very special thank you to the five courageous families who have also offered to share their stories today, so that you may better understand the impact that Canavan disease has on their family's lives. Additionally, we are grateful to the occupational therapist who has experience treating Canavan patients, and will share her professional perspective with you.

We are here today to introduce you to the faces of Canavan disease and increase your knowledge of Canavan. Our role as patient advocacy organizations is to advocate for families and help amplify their stories, especially because there are no approved, disease-modifying treatments for this neurodegenerative disorder. Our hope is that you will emerge from this session with a greater understanding of the disease and the impact it has on the daily life of an affected child as well as the family members and caregivers in their lives – an understanding that cannot be absorbed solely from reading the literature, statistics, and trial data.

Orren Alperstein, President, Canavan Foundation

Ms. Alperstein shared her perspective as a parent of her late daughter Morgan who was diagnosed with Canavan disease in the 1990s and educated listeners about the cause and progression of Canavan disease.

I'll never forget the walk I took up Madison Avenue in the crepuscular October chill in 1990, weeping as I pushed my beautiful eight-month-old in her stroller. I'd just been to the pediatric neurologist for the second time in four months and received the very scary and perplexing news that our daughter, Morgan, our second child, had a demyelinating condition. "She won't do a lot of the things you'd expect her to do," he said. When I'd asked whether she would walk or talk or get married, all he would say was "I can't predict the future."

Nine months later, when Morgan was 15 months old, we received a name for what Morgan had: Canavan disease. Dr. Rapin made this diagnosis after examining Morgan, noting her larger than normal head, her floppiness and high tone, the nystagmus in her eyes, and the fact that she hadn't yet met first-year milestones, like reaching for objects, holding up her head, sitting, crawling, walking, or babbling. She also noted from the form we'd filled out that we had Ashkenazi ancestry. "It will have to be confirmed with a urine test,' she told us, "but I'm 100% sure." At home we scoured the internet and learned a lot of devastating information:

About Canavan Disease

Canavan disease is a rare, inherited, neurological disorder, first described by Myrtelle Canavan, MD in 1931, that damages the ability of neurons in the brain to send and receive messages. This debilitating and lethal leukodystrophy is caused by mutations in the ASPA gene, which makes an enzyme called aspartoacylase. This enzyme, which is primarily present in oligodendocytes, contributes to the manufacture of myelin, and is responsible for breaking down N-acetylaspartate (NAA) in the central nervous system (CNS) and peripheral tissues. The disease also has been called spongy degeneration because the brain degenerates into spongy tissue full of small, fluid-filled spaces.

We learned then that there was no cure for the disease, nor an effective therapy, and this is still true today, more than thirty years later. Treatment is generally symptomatic and supportive.

Most individuals with Canavan disease have the **neonatal/infantile form.** Although these children may appear normal early in life, hypotonia, head lag, macrocephaly, and severe developmental delays become apparent by age three to five months. As they age, children often become irritable and experience sleep disturbances, seizures, and feeding difficulties. Joint stiffness increases, swallowing deteriorates, and some children require nasogastric feeding or permanent feeding gastrostomies. They are socially interactive, laugh and smile, some can reach for objects or operate assistive devices, and are able to raise their heads for a short time in the prone position, but they are significantly delayed in their motor and cognitive skills, and are usually unable to crawl, walk, sit independently, or talk. Early in life there is a decreased ability to visually track objects, and optic atrophy usually develops in the second year of life. Hearing is usually not impaired.

The disease is fatal, sometimes in the first decade of life, but with improved medical and nursing care, children are increasingly living into their second decade, and early adulthood. The financial, physical, and emotional toll on families is huge because these children require constant care.

Morgan lived until the age of seven and a half. When she was alive, there was very little we could do other than to take palliative measures: try to prevent illness with low-dose antibiotics, control her seizures with medication, stimulate her with exercise and social opportunities, and keep her comfortable. And as long as she was healthy, she was a very happy child. She was still able to eat by mouth when she died, most likely of a seizure, in 1997, so she never had a nasogastric or G-tube.

Current palliative measures for individuals with Canavan disease include suction and cough assist machines to clear secretions and mucus, oxygen concentrators for continuous flow of oxygen, and nebulizers to administer medications. Feeding pumps also assist in dispensing liquid nutrients. Positioning equipment like foam supports, feeder seats, specialized strollers, wheelchairs, and bath chairs help patients with their positioning needs.

Over the years technological advances like these have improved the quality of life for those with Canavan and may have extended their lives. Other technological developments, like voice-activated output switches under the guidance of skilled therapists, have also made it possible for children with Canavan disease to communicate non-verbally. Physical therapists have also been tremendously helpful in increasing range of motion, improving endurance, and holding on to gross motor skills, while occupational therapists have provided support around daily movement, cognitive and sensory skills.

There is also a mild/juvenile form of Canavan disease that is even more rare than the neonatal/infantile form.

How is Canavan Disease Inherited?

Canavan disease is inherited through an autosomal recessive disease inheritance pattern, where both parents are carriers for the disease. As with other autosomal recessive diseases, like Tay-Sachs and Metachromatic Leukodystrophy (MLD), with each pregnancy there is a 25 percent chance the child will have Canavan disease, a 50 percent chance the child will be a carrier, and a 25 percent chance the child will be a healthy, non-carrier. Individuals with Ashkenazi Jewish ancestry have a higher carrier rate; two pathogenic variants account for 98 percent of the variants in that community. It is now known that the disease actually appears throughout the general population: One pathogenic variant accounts for 30 - 60 percent of variants in non-Ashkenazi populations, but more than 70 additional variants have also been identified in the broader population.

Early carrier screening programs for Canavan focused on those with Ashkenazi ancestry, and pre-conception carrier screening has been very effective in that population; in fact, the majority of children now diagnosed with Canavan do not have Ashkenazi ancestry. Since many pathogenic variants have been found in the non-Jewish population, expanded carrier screening is now recommended for everyone planning to start or add to their families.

Treatments for Canavan

There currently are no FDA approved treatments for Canavan and the search for a treatment and cure for Canavan disease has a long history. Families have tried various approaches treating symptoms, including targeting the edema with a ketogenic diet and acetazolamide to reduce water concentration. Diet supplementation of acetate seemed promising in rats, but human infants showed no motor improvement. Lithium citrate reduced NAA levels in brain and urine but had no effect on hypotonia and spasticity. Most of these modalities as Canavan therapeutics generally showed good tolerance, however they did not cause any significant improvement in the quality of life in the patients.

It became clear that gene therapy might be the best avenue to pursue. After the gene was identified in 1993, things moved quickly because the researchers involved had already been working on gene therapy for Parkinson's disease: they quickly went from identifying the gene responsible for Canavan disease, to cloning it in the lab, to creating a viral vector suitable for use in humans. The initial procedure involved a nonviral vector, but later iterations used an AAV vector, a very small nonpathogenic virus that does not cause illness, to deliver small amounts of genetic material to neurons in the brain. Subsequent efforts have refined the AAV vectors, and led to two current investigational trials.

Today you will hear from several families who had or currently have children with Canavan disease. Each of their children is unique, but you will perceive a number of similarities in terms of their feelings about their children and their hopes for the future. They are all eager to share their stories.

Parent Perspectives

Parent #1

Hello, I am mom to my two-year-old daughter, P. Firstly, I'd like to say that talking about how P's diagnosis has impacted our family feels strange. Being a parent of a Canavan child, we don't get much time to reflect, we just do what needs to be done. P was diagnosed at five months old. We started noticing the milestone delays and concerns about her vision from around three months old. P was a 'COVID baby', so we didn't get any face-to-face appointments with health professionals after her birth. I was raising concerns with health [professionals], to be told we just had a content baby and she would get there in her own time. It was an unrelated illness that saw P taken to hospital, where a week later the diagnosis was given.

Life after diagnosis has been tough. So many questions, with answers we didn't want to hear. My husband and I were determined to stay strong, or at least pretend to be in front of P and others. Putting on a brave front, I even tried going back to work after my maternity leave ended. This is what I'd be doing without a diagnosis, so that's what I'll still do, I was telling myself. I quickly learned that it was impossible. Juggling multiple appointments, childcare, and a career wasn't working. We decided as a family that I would leave work, which was a bittersweet decision. I get to spend so much time with P, which is amazing. This also means I get more time to concentrate on her physiotherapy and making memories. Downside of course is that it has impacted us financially as a family. Losing a salary and solely relying on Paul's income.

P has regular checkups with physiotherapy, but we do daily exercises at home. We are trying to help build muscle all over her body and keep her joints active. P uses a standing frame daily at home. She found this difficult to begin with, but we slowly built up the time and now she stands happily for up to one hour each day. We have enrolled into a therapy program that uses stimulation of the fascia layer of the body. We have seen positive results in posture of another Canavan child who has been using this type of therapy. We should be starting in the next couple of weeks and hope to see improvement in P's posture and overall strength in the coming months.

It was non-stop researching the disease, which is where I found an article about the gene therapy trial in Ohio. Finding this gave us new hope and something to focus positively on. It definitely helped me mentally to get over the original 'there is no cure' that was playing over and over from diagnosis day. P was asked to go to Dayton, Ohio for some pre-screening tests for this trial. We flew out April last year and were there for a week. P had numerous tests that week including MRI, EEG and spectroscopy. She also had a motor function test and was observed on communication skills. The medical tests showed that P was eligible for the trial, as they found no high-risk factors for the treatment. Unfortunately, we haven't had any news since getting the results on getting the treatment. We remain hopeful, that P will receive this treatment, but every day that passes reduces the likelihood. The treatment is only given to children up to 5 years of age, so we are on a race against the clock, too.

Housing is a big worry for us. We currently live in rented accommodation. Rented housing means we can't have any adaptions that will be needed as P gets bigger, so we know we will need to move. Now down to one income, finding a suitable property within our budget is difficult. Everything here medically in the UK is a fight. I learned that many departments don't [classify] children as disabled until they are three years old. For a parent of a child that can't hold their own head up, I find it astonishing. The relentless fighting with medical professionals is tiring.

We live every day trying to push forward, learning as we go, fighting for P's needs and ensuring she has that beautiful smile on her face as much as possible.

Parent #2

On August 10, 2021, we sat on a Zoom call with our child's neurologist and received the news that no parent should ever have to hear. Our beautiful daughter, with bright blue eyes and an infectious smile, who loves dogs, balls, and her big sister, has Canavan disease.

We probably shouldn't have been as surprised as we were. After all there was always something about N. In the very beginning, she cried. All day long, she cried. We tried everything, but it was clear that something was wrong. We were told it was colic, only later to be told that even colicky babies don't cry as much as N. Around two months we noticed that she didn't smile or look at faces. She didn't track objects or stare at lights like most babies. The ophthalmologist told us that some babies just have delayed vision, and she would most likely just catch up. At six months, she had dropped from the 89th to the 26th percentile for weight and it was becoming evident that she was missing milestones. Oddly enough, it almost seemed like she was losing some. Failure to thrive we were told, probably due to acid reflux. A neurologist suggested that the low muscle tone might be due to hydrocephalus.

A physical therapist suggested that I held her too much. Doctors told me it was because I was breastfeeding, and it was my milk. Friends at work told me not to worry, that their nieces and nephews were late developers, and they were all fine. But deep down inside, I knew that there was something about N.

One of the problems is that N was born during COVID in August of 2020, and many of her appointments, including her neurology appointment, were on Zoom. At one of our first in-person appointments, I could see from the neurologist's face and tone of voice that N's hypotonia was more severe than she thought. She suggested the MRI that gave us the life-changing diagnosis.

That night through our tears, my husband and I read through all the symptoms on Google and realized that finally we were able to connect all the dots. All the things, even things that I thought were just N's quirks, such as how easily startled she was, could be explained by Canavan disease.

My husband and I almost immediately went into problem-solving mode. I began searching through medical journals thinking if I understood the science, that maybe I could help her. We built a care team. Luckily for us, we were able to find doctors with familiarity with Canavan disease. And we started looking at clinical trials.

For the first time possibly ever, there were two clinical trials. One was posted on the FDA website on the exact day that N was diagnosed. We were in the extremely privileged position of having choices, since it appeared as if N met the inclusion criteria for both. But having choices led us to having to make the hardest decision we have ever had to make in our lives.

We knew both trials had risks, potentially serious ones but we weren't particularly concerned about the risks. We didn't know what would happen if we participated in a trial, but we certainly knew what would happen if we didn't. Canavan is a cruel disease. It takes and takes. It takes from the affected child, it takes from the parents, the siblings, the grandparents. There is little left untouched, other than the beautiful smiles of our children who endure so much. We were willing to take the trade-off of the risks of a clinical trial for the hope of something better for our child and our family.

But we had to choose: one trial or the other. Both trials were in their infancy. There wasn't much information or data available to us as to which one would be more efficacious. It felt like a life-or-death decision that we

had to make based on a gut feeling. We took the leap and chose. I told myself over and over again that I would forgive myself if it later appeared as if we made the wrong decision.

The day N went in for her trial treatment she was 22 months old. What I wanted from the experience was to stop the progressive decline. N had a lot of skills for a child with Canavan. She was still eating by mouth. She had head control. She could crawl around on her belly. What I want for N is a quality of life. Being able to eat by mouth and get around the house is a huge part of N's quality of life, but we were already starting to see evidence of the decline.

The decline is the very worst thing that can happen to a parent. Other parents mark their children's lives in milestones, celebrating their firsts with videos and marking it in baby books. The decline is quieter. It creeps up on you. One day you are sitting with your child and you realize that you can't remember the last time they sat or the last time they rolled over. It's just gone, and you don't know when exactly that last time was. There is no baby book for the lasts. Or the decline can be meals that slowly start to get longer and longer. You might not realize it at first, until it hits you that this long meal isn't just tonight, it's been going on for a while. Swallowing has become hard.

Today, N is doing better than I could have ever imagined. But I am pragmatic enough, and I understand science enough, to know that there is a chance that this will not last forever and that these two trials are probably just the beginning in finding a cure for Canavan disease. I am so proud of N and that she is a part of something really important for the Canavan community. We don't know what her future holds, but I have so much hope that science won't forget our kids, that progress will continue, that this treatment will help N get to the next great thing.

Parent #3

My name is Jennie, and I am a Mom to six children, two with Canavan disease: one son, B, who is six years old and our other son, J, who is five years old. B was born in the summer of 2016. I had a normal pregnancy, and a beautiful birth. He was such a good baby. He slept well. He ate well. He had the sweetest disposition.

I soon became pregnant again with J. We were surprised, but felt very blessed. We had wanted to start a family together. It was happening faster than we imagined.

When B was six months of age my sister came to visit. After spending some time with him- she simply asked me- "Does he always need this much head support?"

It was at that age, at six months that B stopped meeting milestones. He never sat up, rolled over, stood, took first steps, or said a word.

But he was very social. He smiled at silly songs. Was happy to see people he knew, gurgled at the right times, during peek a boo. He understood what was going on around him, but his motor skills weren't developing… and as his body grew bigger, his muscles couldn't catch up. He became weaker with every passing month. His head circumference began to grow off the chart. At around 1 year of age, he began regressing. He started struggling to do some of the things he could do before. Like lifting his head up when he was on his tummy. Or sitting in his highchair without added head supports.

Between the ages of six months and 13 months in search for a diagnosis, we saw five different specialists, but B being as social and responsive as he was, confused the doctors. Finally, the third neurologist found NAA in his

urine and called us to come in for genetic testing for Canavan disease. At that time, J was just two weeks old and we brought him along. We were informed that there was a 25 percent chance J had Canavan disease too. So that day both boys were tested, and two weeks later, both boys tested positive for the disease. We were told that children with Canavan disease have three to 10 years to live, and will slowly degenerate. We were told, there were no treatments available, and I quote, "we should go home and make them feel comfortable."

When you look at B and J, you may not know that they are cognitively aware. They often look as if they aren't all there. But they are.

B was and still is what we call, Mr. Chill. He loves to listen to music. He's incredibly social and loves being around people. He just wants to hang out where everyone is. When he was younger, if we had guests over, and we tried to put him to bed, he would stay up even if it was hours past his bedtime refusing to sleep. As soon as we'd bring him to where everyone was, he'd be so happy and engaged. He just wants to be with everyone else.

About a year and a half ago, I was still reading to B the same books I had been reading to him when he was a baby… Suddenly he began complaining when I read to him. Something he always used to enjoy. I asked him… B do you still want to read? Yes. Do you want these books or something different. Different. B was bored! We began reading chapter books, Beverly Cleary, Alice in Wonderland… when asked if he liked them, we got a big smile and his happy sounds. Now, with the help of a reading specialist, B is learning how to read himself using his eye-gaze computer.

For some time, all B wanted to do was walk and take steps. When he'd see his therapists, he'd be so happy because he knew he could work on walking. Unfortunately, this past year he got sick very often and lost a lot of strength. He's working on regaining his ability to take steps now.

We call J the busy-body. He is always listening to everyone. He hears when he's upstairs and his Papa comes home from work. He will stop and turn when he hears his older brother come home from school waiting for him to say hello. He will squeal loudly in delight if he hears me talking on the phone to my mom- because he wants to talk to Grandma, too! If I mention a doctor's appointment, in a conversation he'll look at me and vocalize in his questioning voice, wanting an explanation.

J has a big personality. He is so determined and stubborn, he will try and try when he wants something. He has often surprised me with his cognitive and physical feats. Here he is matching the sight word "Be" from a few different choices.

Their beautiful minds are trapped in a body that is so disabled, so medically fragile. They have a list of diagnoses and specialists that care for them, that is too great to review now… but it makes participating in life for them and for us as a family a daunting challenge. It's difficult to go enjoy everyday life because of all the equipment needed. As well as being able to prepare and pack for their feeding, medication and lung treatments, and having the manpower to carry and implement it all. Everyday things become a project, like going on a family walk. It's a struggle to find the strength and resources to keep them involved.

We were told there was no treatments available. That we should go home and make them feel comfortable.

After their diagnosis and a few weeks of intense mourning and depression, we decided we couldn't sit by and wait. We spent weeks researching. We found a researcher that was working on a gene therapy treatment for Canavan disease, but the trial was stalled.

My husband and I both left our businesses to focus on getting treatment and we began working on a clinical trial right away. Every day counts with a rapidly progressive disease. Starting a clinical trial with no prior experience in the field and no funding was … crazy… and at times felt impossible. We spent sleepless nights fundraising. Somehow our campaign went viral, and we opened a charity, Cure Canavan Fund, in early 2019. It took four and a half years, close to 6 million dollars, and a lot of help from specialists to get there, but we did. In April 2021, B was treated with gene therapy and then J in June.

Since then, their MRI's show remyelination and new white matter growth. Their vision has markedly improved, as has their motor function. It has certainly slowed down the progression of their disease. It's given them a better quality of life than they had before. Since the treatment we see improvements instead of only decline.

Being a mom to B and J has changed all of our lives on every level. Having such difficulties with every level of function in your body, is so hard, but it has really opened up my field of vision. I appreciate what I would have never seen or appreciated before.

Parent #4

Hello. I am Amy and the mother of two amazing boys. C, who is 18 years old, a senior in high school, my comic relief, and often my second set of hands. And L, my beautiful 13 year-old son affected by Canavan disease. L is smart, funny, soulful, and wears his heart on his sleeve. At only 13, L is considered an "old" Canavan patient. Can you imagine that? My youngest child has been on this earth for a mere 13 years and in the Canavan world, is considered "old".

L was nine months old when he was diagnosed. We were devastated. Our world changed in an instant. All the dreams I had of one day my boys running around together, confiding in each other, rolling on the floor laughing, fighting, growing old together, all of it died that day. I had to put on a new kind of mom hat. I had to shelter C, five years old at the time, from the truth until he was old enough to understand. I learned very quickly how to be two kinds of parent. From that day on, I have been the mom who lives in the moment and talks to my kids about how amazing life is and how bright their futures are; and at the same time, the mom who is silently scared to death every single day that I will wake up to find that Canavan disease has taken L from us while we were sleeping. This is reality. I try to mentally prepare myself for that day, as much as anyone can prepare for the loss of their child.

I live in two realities, really. I know the facts about this disease. What it is doing to my son, but I also believe in miracles. L has been amazing us his entire life. When he was a baby, we saw red flags that included inconsolable crying, head would not turn toward noises. There was no smile when we entered the room. He could not keep a fixed gaze, and he could not hold his head up.

Leading up to his diagnosis we were told...
"He is non-responsive.
Whatever is going on cannot be surgically fixed.
Do you have family close by for support?
There is no cure, only comfort care.
Some kids live to two years old, some kids live to four.
He'll never be able to communicate with you."

And the most insensitive comment of all, *"If you choose to keep him with you, you will never have a normal life."*

"If you choose to keep him with you..." That one floored me.

He is funny, kind, stubborn, ridiculously smart, loves math, and has a passion for whales. Since age seven, he communicates using a laser pointer taped to the bill of a visor and an alphabet board placed in front of him. With his head supported, L started to spell small words by moving his head and hovering over the letter he wanted. When asked "Do you want to say anything to mama?", letter by letter, my seven-year-old son spelled out I L-O-V-E Y-O-U. I felt those words like he was speaking them to me. I cried so hard. It was amazing. The next thing he spelled out was to his dad: A-R-E-N-T Y-O-U P-R-O-U-D O-F M-E? then [a message] to his brother. A whole new world opened up for us! We started full-on conversations. And now, he writes. He writes entire stories. He needs my help holding a marker or pen. I place my hand over his hand, unweight his arm and he forms letters into words, into sentences, into stories, or ideas, or questions, or tells us what's bothering him. He shares his thoughts. We communicate, and it's awesome! He is so much more than what you see.

I had to pull him out of school at the end of fourth grade and start homebound services because his medical needs were increasing, and our county wouldn't provide a one-on-one aide or a nurse for him. He used to love going to school and spending the day with his friends, and they loved him. He misses them. If his head dropped forward from a sneeze or when his entire body stiffens up, he doesn't have the strength to lift if back up and his airway is cut off. He frequently needs suctioning to clear his airway due to an increase of secretions. This often causes him to vomit which then requires more suctioning. He has a seizure disorder. Sometimes up to eight seizures a day. He is on two different medicines to help manage them. The seizures need to be timed, and rescue meds administered if they last more than five minutes or if he has a cluster of them within a few minutes. It was not safe for him to be at school. His physical and occupational therapists and the nurses at the hospital are his friends. We spend half of his life in the hospital. At the end of fifth grade, we were still doing homebound school. He wasn't invited to the graduation ceremonies. This short video shows his fifth grade graduation ceremony at home. We're planning his next one this year when he graduates from middle school. You all are welcome to come.

Life with L has many ups and some downs. We have found our flow, but physically, it's hard. Really hard. L, at age 13, now weighs over 80lbs. We carry him to get him where he needs to be. To bed, to his wheelchair, to the stairlift. I am worried about the day he gets too heavy for us to lift. I really don't want one more piece of large, impersonal medical equipment in my home, but that day is coming. He can't use the toilet. Every evening we give him senna and lactulose, and every morning he gets an enema so he can move his bowels. Canavan disease has given him a neurogenic bladder. He has stage 3 kidney disease and Renal Tubular Acidosis. We were averaging eight urinary tract and kidney infections a year so L now has a vesicostomy where a hole placed about two inches below the belly button, at the top of the bladder and his urine flows into a diaper or pad directly out of that hole. It's usually done in babies, not 12- or 13-year-old kids. We need to change the pad every three hours, or it gets too full. He has a g-tube that runs continuously so he gets enough hydration and nutrition because he is unable to chew food and could aspirate on thin liquids. I am grateful for the g-tube because at the age of seven, he was labeled underweight and "failure to thrive". We haven't gone swimming in two or three years because the sudden temperature change of the cold water would make him throw up. L loved the water before that started happening. We regularly see a neurologist, a nephrologist, a urologist, a gastroenterologist, a pulmonologist, an ENT, a physical medicine doctor, and now an epileptologist.

I asked L what he likes about himself. He wrote "I like my wheelchair. It makes me wheely cool".

We all selfishly want L to be able to be more independent and to live a long, happy life. If I could wish any of this away, I would wish for C to not feel the heaviness of worry. I would want him to know that L is the happy kid he is in large part because of how much his big brother loves him. I would want L to have the strength to hold up his own head and for the suctioning needs to be controlled. I want life to be easier. I want to plan vacations without needing to know where the closest emergency room is.

Our lives with L may always have these struggles, but we take comfort in knowing that L is happy. Maybe that has to be enough.

Parent #5

My name is Abby and my son B was born on October 12, 2001 in Washington, D.C. When he was born, he was a big, beautiful baby and was seemingly completely healthy. The OB resident that discharged us from the hospital said to me, "Just be thankful that your baby is healthy. I see many that are not."

Little did I know our baby was not healthy at all. In six short months when babies would be learning to sit up, hold and mouth toys and squeal, my husband and I would be told that B was affected by Canavan disease.

B began to cry all the time, from the time he woke up until he drifted off to sleep exhausted. We rocked him, went out for walks, had various types of music on repeat, and gave him frequent warm baths. Nothing seemed to help. We sought advice from B's pediatrician, and he suggested we supplement breast milk with baby formula. This did not help with his discomfort. His pediatrician appointment at two months and beyond showed relatively normal growth, but an increase in head circumference, which was noted by the physician. Also, noted by his concerned parents was very tight leg muscles in his upper thighs, it was hard to relax his straight legs to change his diaper at times, he seemed rigid and stiff and not moving the same way we observed wiggly babies his age moving and reaching for toys.

My husband and I grew more concerned as B seemed uncomfortable. I remember saying to B's doctor that he did not seem to be making eye contact, and he was no longer smiling which he had started to do right on time developmentally. We were eventually referred to a pediatric neurologist with a two-month wait. B needed to be held 24 hours a day to be consoled.

The DC summer heat seemed to make things worse for B, his head got larger, and he constantly seemed like he had a headache. He no longer had the head control he had at two months; his head would drop forward when in the Baby Bjorn carrier. We thought something was wrong with his neck muscles.

Two weeks out from our specialist appointment, and becoming more and more attune to his every move and cry, my husband and I became detectives and tried endlessly to soothe B. One afternoon, as we put him down for a nap, he had what I thought seemed like an unusual movement, like a jerky seizure movement. We took B to the ER, looking for answers. The ER doc said B was not visually tracking and ordered a head CT which showed an abnormal myelination pattern in his brain which we could tell from the intensity of the discussion with us that this was not good and indicated developmental problems. Kennedy Krieger Institute diagnosed B with Canavan disease at six months of age.

Canavan disease is a cruel disease. As an infantile neurodegenerative condition, B has severe intracranial pressure and posturing, and he was hospitalized. This caused his intense fussiness. His head hurt. B was

prescribed a medication to help, and things settled down a bit and at one year B's smiles and laughs returned. This was the best thing for us as parents. We did not know if we would see his smile again.

B had spasticity (hypertonia) in his legs and arms and floppy muscle tone (hypotonia) in his neck and trunk which affected his airway and breathing. He lost the ability to coordinate sucking and swallowing effectively which resulted in his requirement for a g-tube in order to keep him hydrated, and receive nutrition through enteral formula. The g-tube was one of the first big intervention decisions my husband and I made for B at 18 months of age. What we originally resisted conceptually we embraced as one of the best decision we made for him to keep him healthy and enable him to take up to 15 different medications daily to prevent reflux, seizures, spasticity, neurogenic bladder, kidney stones, and special specific medications for Canavan symptoms and most importantly as he got older medications for pain relief and sleep.

From age three to six, B developed apneic seizures which required frequent hospitalization until they were brought under control and at which time, they became very infrequent with daily medication use. Respiratory illnesses were very difficult for B. He was hospitalized frequently for common childhood respiratory illnesses, was very medically fragile, and was home schooled. He did both private and school-based physical therapy, occupational therapy, and speech therapy. B was non-verbal and had low vision. We do not believe he was able to process what he saw, and he had nystagmus. He did, however, have extremely acute hearing. He knew his Mom, Dad and little brothers and smiled and laughed. He was very socially attuned and loved to be the center of attention. He loved funny sounds. He loved all types of music, especially Johnny Cash.

After the age of 8, B had a hard time controlling his body temperature in the summer heat. He could not be outside when it was hot, and as he got bigger was not comfortable sitting in his adaptive stroller for an extended period of time. He was most comfortable in a reclined position where his head was supported to keep his very fragile airway open and supported. We had full-time nursing at home as B needed assessment frequently for his respiratory status. B needed daily nebulizer treatments multiple times a day, followed by vest treatments, which helped break up the serious cycle of excess mucus, and lung infections. B required frequent suctioning to keep his airway clear of secretions. As B got older, he had more orthopedic needs to prevent contractures, including AFOs and wrist splints. He developed scoliosis. He later was treated with Botox® (onabotulinumtoxinA) and phenol injections to help with his spasticity and to keep him comfortable.

We tried to keep B as pain free and as happy as possible. For us, that meant no unnecessary invasive procedures unless they were necessary to relieve discomfort. After the age of 11 he required a memory foam mattress and frequent repositioning to avoid skin breakdown, more and more frequent respiratory interventions to keep him at his baseline and more and more medication changes to keep him comfortable. It became harder and harder to keep his weight stable as his growing body struggled to digest more formula. He was still a very happy boy despite all of his physical struggles. He reliably was healthier in the spring and summer when illnesses were less and as a result, we planned outside time for him during the better weather. He was no longer comfortable being moved much from his bed or his comfy couch. He was very fragile.

At the age of 12, and wholly unexpectedly B died on August 30, 2014, due to a sudden respiratory complication of Canavan disease. We loved our handsome, sweet natured, ever so patient B, who had that "special something" so often remarked upon by others. Was it his bright blue eyes that told a thousand tales? His smile which always reassured us? Maybe it is his melodic sigh? It was combination of all of these, we think, starting in his very center with his open and hopeful heart. Thank you for the opportunity to share his story today.

Occupational Therapist

I'm an Occupational Therapist, and I've been treating B and J since they were babies. Both boy's therapy journeys, and therefore my experience treating them, has been different and unique. In the early years, both boys worked really hard in therapy and made progress – but I always felt like I was helping them race as fast as we could up a down escalator. Though it felt like we were overcoming the down escalator, any time life events caused a gap in their therapy services we saw the race get slower.

B started treatment at age six to seven months and was already a victim to the pull of gravity. He had a hard time moving his trunk, head, arms, or legs in any position. It was clear that he wanted to play and wanted to engage, but he just couldn't. Because his motivation was so high, he worked really hard in therapy. Providing support and positioning helped him learn to reach and interact with toys, allowing him to experience the joy of play.

J was a different story as he started therapy at two months old. While Canavan disease was definitely apparent in his early months, we were able to work on getting a head-start while it seemed like the down escalator was going slower. While B's motivation had been to cognitively explore a toy, perhaps having never really felt movements in the same way, J reveled in the sensations of moving, touching, and feeling. J loved being helped into developmental positions, moving around on the therapy ball, zooming around in therapist arms. Though quality wasn't perfect, and he often fatigued after a few minutes, J was able to hold his head up, sit propped on his arms, roll over, and stand with assistance. He loved to reach out and touch things. He loved to dance, and I loved that he had enough motor control to express that.

Both boys made progress and enjoyed the benefits of improving their motor skills to whatever degree they could. Interacting with the world around them helped them learn, grow, and participate meaningfully in their daily lives.

When regressions hit, though, it was often devastating for the boys. Often when there was a break in therapy for whatever reason, we saw the regression. B had a prolonged hospitalization and a hard time recovering at around two years old. Besides for the physical recovery, his self-regulation and mood took a hard hit. The previously happy little boy was now often unhappy. Besides the trauma of a hospitalization and illness, he "returned" to a body that wasn't able to do the same things that it had been able to do before. We had to work really hard to try and regain some strength, but this time he wasn't as willing. He spent weeks screaming at therapists and having a hard time engaging in therapeutic activities. Eventually B did enjoy therapy once again, and we continued to fight our way up that down escalator.

J, being the more "sensory seeking" boy, became very anxious as his body changed. For a child who struggled with sensory regulation, he couldn't rely on what his body could do and how his body felt. J was often anxious and uptight. I can't imagine what it felt like as holding his head up, sitting, and standing became harder and harder for him. While he used to move himself around by wiggling on the floor, or rolling on his own, he wasn't able to do these things anymore, and it was devastating to watch, powerless, as the down escalator, our constant enemy, started to win over our early head start.

Both boys participated in a gene treatment study around two years ago, and their quality of life improved tremendously since then. B, who had never really been able to move his body freely, began to wiggle around. His joy was palpable, and his mood improved tremendously as he became able to participate in his daily life more fully. He enjoyed working on sitting up, standing, and reaching in therapy. Therapy was easier, as now I could help him sit with less effort from me, allowing me to help him reach and play more easily. J, on the other

hand, took some time recovering from surgery, but he made strong improvements in his ability to control his arms and play with toys. As his body had changed again, we worked in OT on feeling comfortable and secure with his new motor capacity as we worked on activating his muscles for improved skill. He made progress in his ability to participate in and play in daily activities, and his mood has also improved tremendously.

In the years since, we have been working hard to keep getting stronger and keep up with their growth, so that they can continue to participate in daily activities as much as possible. Childhood viruses and breaks from any of the therapies in their schedule can cause setbacks. B learned to stand up and take some steps with therapist assistance, but because of decreased practice due to staffing issues and quite a few large growth spurts, it has become harder for him. The hope is there that we are going to gain that ground back.

J has been making steady progress and is able to use his arms to play and show us how smart he is. He is working on standing and his head control in sitting is progressing nicely. Both boys love to engage with the world around them but need ongoing support and therapy to enable them to do so.

Themes and Q&A Discussion

Themes that arose throughout the parent statements:

- Similar diagnosis experiences with early symptoms including inconsolable crying often compared or worse than "typical" colic, development delays, vision issues.
- Children have clear personalities that are distinct.
- Head control is a factor in quality of life.
- Importance of physical and occupational therapy to children affected by Canavan.
- As children get older, the more limited families are in going out for a simple walk, a day at the beach, or away on vacation.

Q&A from the FDA

Is the gene therapy trial age limited? It looks like the older boys have not gotten the treatment.

Parent #3: Trial A's age criteria is up to five years.

Parent #2: Trial B's age criteria is under 30 months.

Thank you for sharing your stories. If there was an area that it was possible for a new treatment to change, what would that be for you?

Parent #4: She said it was really hard to narrow it down to any ONE thing, but if she had to choose, she would hope for L to be able to hold his head up on his own. That affects so many facets of his life, even taking a walk. Any bump can cause his head to fall forward, which can cause headaches and breathing issues. She believes head control would be the most impactful.

Parent #5: She agreed with Parent #4. B lost the ability to hold his head up after two months, as well as head control other developmental milestones, being able to turn, sit up, etc. Without head control, respiratory and swallowing issues also develop.

Parent #3: For her, it would be motor function, which she admitted was general. She also believes communication and being able to verbalize thoughts and feelings are also very important for children with Canavan.

When thinking about a potential treatment for Canavan, what is one daily life activity, which would you want to preserve and why?

Parent #4: L really enjoys his walks, and he likes being able to go out as a family to festivals or the beach even as he is confined to a wheelchair. As he grows, it's harder to go out, and the fear of being trapped inside their home is life-limiting. Their neighbor allowed for a path to be built between their properties, so they can use their neighbor's driveway to go out for walks, since their driveway is too steep. L is too heavy to push up and down the driveway.

Parent: As M got older, the repeated infections and illnesses were overwhelming, especially upper respiratory infections. She also had frequent urinary tract infections. It would have been nice to have more control over those periods of sickness.

Parent #2: N can play now with her older sister since being dosed in a gene therapy trial. It's wonderful that she can play and have autonomy over what she plays with and how. Even being able to squabble with her sister is appreciated. They have "learned how to lean into not having answers."

Parent #3: Biggest difficulty is not being able to participate in activities outside of the home. Being a family with six children and two of those children needing so much equipment, aides, wheelchairs, etc., it makes it challenging to get out. It is very limiting.

Your stories are amazing and thank you for coming out. Would anyone like to talk about the risks in participating in a trial? They (The FDA) are currently looking at it from a public health standpoint. What does risk feel like to you?

Parent #2: The disease is dreadful. It takes so much from families. Speaking for themselves, they read all the studies (i.e., liver toxicology), talked to all the doctors. There are awful risks, but they shared that they knew what the path looked like without the trial—children die from Canavan. So, the choice was clear. They were willing to take on the risks.

Parent #3: At first, before they understood Canavan, they didn't want to [make any choices that would] prolong suffering. But, seeing how the children have so much enjoyment and are cognitively aware and so intelligent, it is now about preserving the beautiful life they have. There was no choice at that point; the parents wanted to help the children live the fullest life. Treatment would be preserving a wonderful life. It didn't seem like a risk. They know what would happen if they did nothing.

What would be (are) the challenges of participating in a clinical trial?

Parent #4: L does not meet the criteria of current trials. He is too old. It is a struggle because mom wants the same things as the younger children who qualify today. It is 1000% a race against time. She encourages families to "find that door to help kids communicate" with them. If a trial opportunity came up, she would consult with L and ask him his opinion about participating in the trial. He is cognitively aware and can communicate, so she would give him the respect to decide.

"Never is not an option. He is valued. We don't talk about can't. He likes who he is. He's not less than." When he was in school, he was the last one to get a set of hands to help him. He was last in line because of his wheelchair.

She spoke about what L currently "can do" and fears that any trial could possibly take that quality of life away. He may lose what he already has.

Parent #5: B was born in 2001 when there was a gene therapy trial ongoing, but it was focused more on the delivery approach, not a curative situation. Science has come a long way, and the choice today would be different, particularly as it is less invasive. It is an exciting time now. Mom shared that, although she and her husband did not pursue gene therapy for B when he was young, they would have considered it if the current [more scientifically advanced] gene therapy trials were available then.

Parent #3: Both she and her husband left their businesses to pursue the clinical trial they participated in. It is a full-time job, and when they have follow-up appointments out of state, the whole family travels with them. Canavan has turned their lives upside down, and their entire family focus revolves around B's and J's needs and schedules.