Larry Bauer, RN, MA (00:14:33):

Good morning and welcome everyone to the Externally Led Patient-Focused Drug Development Meeting for Cerebral Creatine Deficiency Syndromes. We're so happy that you could join us today. My name is Larry Bauer and I will be the meeting moderator. It's my pleasure to introduce my co-moderator, Heidi Wallis. Heidi is the executive director of the Association for Creatine Deficiencies. Heidi holds a bachelor of science degree in business management and prior to working for ACD, Heidi worked as a grant analyst and project manager in the Utah Newborn Screening Informatics Program and serves as a member of the Utah Newborn Screening Advisory Committee. Heidi lives in Salt Lake City, Utah and joins us here today in studio in Falls Church, Virginia. Good morning, Heidi.

Heidi Wallis (00:15:26):

Thank you, Larry, and hello everyone. Welcome to the Externally Led Patient-Focused Drug Development Meeting on Cerebral Creatine Deficiency syndromes or CCDS. My name is Heidi Wallis and I'm the executive director of ACD, the Association for Creatine Deficiencies. Our mission is to accelerate the development of treatments for people living with creatine deficiencies, including ACAT deficiency, GAMT deficiency, and creatine transporter deficiency, or CTD. A special welcome to the many staff members of the US Food and Drug Administration that are taking the time to be with us today. Thank you for giving us permission to hold this meeting. We're excited to have you with us and hope that you will learn a lot today from our amazing parents, caregivers and even a patient or two. Thank you to our sponsors, Ultragenyx and Sarah's Brain Therapeutics for their generous support. We are very pleased to have in attendance representatives from advocacy and professional organizations, pharmaceutical companies, federal agencies, and research centers from across the world.

(00:16:39):

Thank you for joining us today. But most importantly, I want to welcome the members of the audience whose lives have been directly impacted by a CCDS. Today's meeting is the result of many months of planning and people working together behind the scenes, and I want to extend my deep gratitude to everyone who has had a hand in preparing for this meeting. We are grateful to have this opportunity to ensure patient and family perspectives are considered in the drug development and regulatory processes. CCDS have a severe impact on quality of life, affecting our children in ways that can be difficult for people outside of our families to understand. Most of our children have no or very little speech, and therefore are not able to tell their own stories or advocate on their own behalf. Many of our children are further affected by behavioral difficulties, sometimes so severe that they and their families experience social isolation.

(00:17:43):

As you will hear today, many living with CCDS are severely affected by developmental disabilities. Others experience epilepsy, sometimes resistant to therapies, often hypotonia, sleep problems, and gastrointestinal problems further diminish health related quality of life for creatine deficiency patients. Despite these severely debilitating manifestations of CCDs, there are no FDA-approved treatments for any of these disorders. As an example, two of my own children, Sam and Louie have GAMT deficiency. Their treatment consists of supplements ordered online, measured and mixed at home, and they'll tell you they taste terrible. Although their creatine levels are replenished with this therapy, guanidinoacetate, a neurotoxin remains elevated and our family is just one of hundreds concerned for our children's futures. As I said before, there are no FDA-approved treatments for CCDS, but we hope

you will remember the stories you hear today. They're just a small number of our worldwide community and that you will remember the great needs that exist for treatments for creatine deficiencies.

(00:19:06):

I want to express my appreciation to the investigators working in labs all around the world, striving towards a better understanding of basic and translational CCDS science and moving us closer to future clinical trials. Our hope is that this meeting will encourage future research and successful new product development for people living with CCDS who urgently need treatment options.

(00:19:35):

For our CCDS families, we invite you and your loved ones to call in or write in during the program and we ask you to stay with us and participate in the polling throughout the meeting. We want to hear as many perspectives as possible and we'll do our best to get to as many of your comments as possible. When participating today, please only use your first name. Be assured that any comments that we're unable to get to, they'll still be very important and we will include them in the voice of the patient report, a summary of this special day. So to begin today's meeting, I am delighted to introduce our speaker from the FDA, Dr. Anna Choe. Dr. Choe works in the Office of Tissues and Advanced Therapies in the Center for Biologics Evaluation and Research, or CBER, at the FDA. This is the part of the FDA that regulates cell and gene therapies. Dr. Choe will provide some opening comments from the FDA perspective. So, Dr. Choe, over to you.

Anna Choe (00:20:47):

Hi, good morning. I am Dr. Anna Choe. I'm one of the physicians in the division of Rare Diseases and Medical Genetics at the FDA. I will be providing a brief overview of the Patient-Focused Drug Development Initiative and share my experience with the PFDD meetings. Before I begin, I'd like to really thank the patients and caregivers for making time to share your experience with us today. I'd also like to thank the Association of Creatine Disorders for organizing this meeting and inviting us to listen and learn. This is a disclosure slide stating that this presentation does not convey official FDA policy and that I do not have any financial interest or conflicts of interest to disclose. To discuss the value of patient input and drug development, we really have to start with the mission of the agency. The FDA is responsible for making sure that drugs, biological products, and medical devices are safe and effective. The FDA is also responsible for helping encourage innovations, so that these products are more effective and safer, and also helping the public get accurate and scientific information, so they can use this information to utilize them, the drugs and biological products to help their own health. To achieve this mission, the agency really stripes incorporate the patient's perspectives from the beginning of the drug development to the end in every step of the way. So early in the development phase, in the basic science phase, patient input can help us identify outcomes and endpoints that are the most burdensome or meaningful to patients. And, this is really important for us because you are the experts of your disease and your daily lives.

(00:22:38):

So, hearing from the patients through registries, natural history, these PFDD meetings and FDA listening sessions are extremely informative for us. During the clinical studies phase, your input on clinical trials, sharing your willingness to participate in clinical trials with placebo arms, hearing about the different barriers you've identified such as travel distance or route of administration can help us design better clinical studies. This is also really important for recruiting and retaining study participants, which is particularly important for our division because so many of our conditions are rare and have small patient

populations. In the pre-market review phase, we integrate patient reported outcomes and patient preferences and in addition to other data that's made available from clinical trials to think about the benefits versus the risks. And in the post-market phase, your input can help us communicate more clearly the information you need to make decisions regarding the drugs and biological products that have been approved.

(00:23:46):

So an externally led PFDD meeting, which is what we're having today, is one component of the Patient-Focused Drug Development Initiative where patient groups or organizations organize meetings to provide public input on specific diseases. I have been with our division for a couple years now and I've attended several PFDD meetings and it's been extremely helpful to hear the firsthand experience from patients and caregivers. It's been really helpful for me to hear about the symptoms that are the most bothersome, outcomes they like to see from treatments, and hear about the currently available treatments. Many of the conditions have very unique treatments that may not be regulated by the FDA, and it's helpful to hear about what the gaps and challenges are with the treatment regimen. So, there are a couple websites that are available here. After the meeting, there will be a voice of the patient report generated.

(00:24:42):

It'll be available on the website and it'll be also available for other stakeholders to access. So the work you do today, what you share today will be used by other stakeholders who may not be able to attend the meeting today. There's also an email address available if you have any questions to follow up. We are really grateful for this opportunity to hear from the patients and caregivers. Thank you so much for your time and your willingness to share your experience with us. I'm looking forward to hearing from you and learning from today's meeting. Thank you and back to the studio.

Heidi Wallis (00:25:19):

Thank you so much, Dr. Choe. Next up is Dr. Andreas Schulze to provide a clinical overview of CCDS, which will serve as a scientific foundation for today's discussion. Dr. Schulze is a well established CCDA expert and clinician scientist who has spent more than 25 years in medical research and clinical care in the field of inborn errors of metabolism, mostly at the Hospital for Sick Children in Toronto, Ontario. He has a deep interest in understanding the biochemical and molecular basis of disorders related to creatine metabolism and has developed a research group dedicated to these efforts. Dr. Schulze, over to you.

Andreas Schulze, MD, PhD (00:26:07):

Thank you very much for the very kind introduction. I'd like to give you today a brief overview about conditions called creatine deficiency syndromes, but before I do this, I have some disclosures. I'm on several advisory reports, but I'm also a site PI on a number of clinical studies funded by industries like Aeglea, Moderna, Ultragenyx. So, I'd like to start off with something that we usually do as clinicians, and this is I present a clinical case. This girl is the sixth child of healthy consanguineous parents. There was unremarkable pre peri, and postnatal period, and then it was around the age of six months that parents noted some delays in her cross motor development. She was not able to sit or crawl at the age of 15 months and it took her until two and a half years where she could start standing and walking, but supported. At three years of age, family recognized some loss of acquired skills.

(00:27:21):

She was not any longer able to sit and pull up. She lost social contact. She stopped playing and most obvious was a seizure disorder that started at the age of 14 months with an long febrile seizure, but then progressed to an untractable epileptic syndrome. So, that is her, and this is when she was almost four years of age. She had microcephaly, was not able to sit or pull up herself. She also had an extrapyramidal syndrome with some dyskinetic-dystonic movements. She had increased muscle tone and deep tendon reflexes. Also, some myclonic jerks. When we did some basic investigations like MRI, we found some delayed myelination, but nothing else. Abnormal EEG showed the epileptic discharges. Neurophysiology was normal, and in laboratory we found some ammonia and some lactate, and the lactate was the reason why I went with her for brain spectroscopy to see whether she has lactate in the brain.

(00:28:43):

And, that is how we made the diagnosis because what you can see here, there is basically no creatine peak, and usually creatine is one of the three large peaks in brain MRS spectroscopy. There were other clinical findings, mainly in urine. We found very low creatine, or not creatine, but creatine and very high guanidinoacetate, but also liver abnormalities where identified the mutation, confirmed that she has guanidinoacetate methyltransferase deficiency. And so, she was one of the first two patients in the world diagnosed with such a disorder. So, what I'm going to do is I will talk a little bit about some creatine basics, and then I'll talk about the three creatine deficiency syndromes that we know: GAMT deficiency, AGAT deficiency, and creatine transporter deficiency. Clinical presentation of those sweet disorders, the diagnostic tests that we are using, and I spend a few words about newborn screening.

(00:29:54):

So, we talk about creatine deficiency, and when I started with this group of disorders, I googled creatine, and that's what you find. This was in 2002 when I took those pictures, but you'll find the same today. Creatine is well known and it is used as a supportive to improve muscle strength, and a lot of money is paid on this, but we did not expect that creatine when it is deficient, causes something completely different than muscle problems. So, what is creatine? Creatine comes from Greek means meat. It is a short molecule, it has a guanidino group. And, why do we need this?

(00:30:54):

Creatine works in the system, phosphocreatine, creatine kinase system, but basically transports ATP from the site of production to the site of consumption, and creatine is circled back. So, we don't have a consumption of creatine. And this system is important, it is an energy transducer and it works as a buffer both temporarily and spatially for energy provision. So, the system of creatine is one of the phosphagen systems, and it is as old as the animal kingdom. Since more than 5 million years, we do have creatine and we use creatine for this purpose and only since the diversion between the invertebrates and the vertebrates, we have a group, and this is the vertebrates that are not only able to extract creatine from the environment-

PART 1 OF 10 ENDS [00:32:04]

Andreas Schulze, MD, PhD (00:32:03):

... that are not only able to extract creatine from the environment, we are able to produce creatine as well. So humans, the prehistoric hunter for example, would eat three kilograms of meat a day and basically provide all the creatine needs by food. But there were also already then people on the vegetarian diet and they would basically ingest almost no creatine and they would rely on endogenous creatine synthesis.

(00:32:32):

So we do have two sources for the intracellular creatine provision. One source is creatine synthesis and the other is creating uptake and they work together. Creatine synthesis consists of two chemical reactions. First chemical reaction is the AGAT reaction using transferring the omithine group from arginine to glycine and that leads to the formation of guanidinoacetate. Then guanidinoacetate acetate gets a methyl group from S-adenosylmethionine re AGAT reaction and that forms creatine. The other way to maintain intracellular creatine homeostasis is by the action of the creatine transporter, SLC6A8. So now I talked about the three creatine deficiency disorder. The first one that had been discovered was in 1994. It was Dr. Stockler working close to the German town where I was working and I had the second patient. So basically at the same time we found two patients that had basically no creatine in the brain and that led to the discovery of GAMT deficiency. It's an autosomal recessive disorder. It is a rare disorder.

(00:34:09):

We at least nowadays know more than 100 patients with this condition. Estimated prevalence data is in a range of perhaps one in 500,000, one in one million, but we don't have data that would reliably tell us how frequent it is. So this is GAMT deficiency. What you can see is when you have a deficiency of this enzyme, GAMPT, then you get deficiency of creatine, but you also get the buildup of the precursor and this is guanidinoacetate.

(00:34:54):

The second condition was identified, reported for the first time approximately six years later, is AGAT or arginine glycine amino transferase deficiency. It is also an autosomal recessive disease, but we know only a couple of handful patients so far, perhaps 20 worldwide. So this condition is the first step in creatine synthesis, the AGAT reaction and the consequence is a deficiency of both guanidinoacetate and creatine.

(00:35:37):

The third condition is the most frequent, and you can already see this on the number of genetic variants that have been identified, and this is creatine transporter deficiency. This condition is X-linked, also described around 2000, and we know way more than 200 families now. So frequency is perhaps in a range of one in 200,000, something like that. Since it's X-linked, it's mainly boys that are affected.

(00:36:17):

So what is the consequence? The consequence of transporter defect is that there is no uptake of creatine in the cell. This may be compensated in areas where creatine synthesis can compensate for that, but obviously some areas, and mainly the brain, is not completely self-sufficient in creatine synthesis and relies on creatine uptake.

(00:36:45):

So I go to clinical symptoms. I mean you have seen this video clip at the beginning that demonstrated how those conditions are looking like. But all of those, and I put them together because they have most of it in common, and this is for example, a predominant speech disturbance that is almost no expressive speech and restricted comprehensive speech. That's common for all.

(00:37:22):

Other problems like behavioral problems, like autistic-like behavior and also some muscle problems also, and mild EEG or epilepsy changes. This is what all have in common. When you ask or wonder what is the difference between those conditions, perhaps the most striking difference is that GAMT deficiency can

present with a severe epileptic syndrome that is refractory to any treatments. That's different to AGAT and creatine transporter deficiency. But there are also extraneural symptoms, and this is for example, GI symptoms can happen or failure to try feeding intolerance. But in general, all of those are mainly neurodevelopmental disorders.

(00:38:23):

Next is how do we diagnose this? We can diagnose AGAT and GAMT deficiency easily by blood tests, measuring guanidinoacetate and creatine. In AGAT GA is low and creatine is low. In GAMT GA is highly elevated. For creating transporter deficiency we do a urine test where we find an increase of creatine to creatine in ratio.

(00:38:54):

All conditions can be identified by MR spectroscopy in the brain with 100% sensitivity, seeing there is a creatine depletion and can do target gene sequencing. Most of the time now patients are diagnosed by whole exome sequencing and biochemical tests measuring enzyme or so are not any longer much in us.

(00:39:20):

So the last part of my talk is about newborn screening. GAMT deficiency is, if untreated, a severe neurodevelopmental disorder with irreversible brain impairment. If we treat patients early, we get normal development and improved outcomes. So that is perfect for a newborn screening condition and we do have a newborn screening assay that is reliable and cheap.

(00:39:51):

Therefore, several jurisdictions in the world have started newborn screening in the past like in Australia, in British Colombian in Canada and in three states in the US, Utah, New York and Michigan. But more recently the advisory committee of heritable disorders in newborns in children has recommended to the United States Secretary of Health and Human Services to add GAMT to the recommended uniform screening panel in the US. We have started new newborn screening in Ontario. AGAT deficiency is, when early treated again, causing a normal or preserving a normal development, but we don't have a reliable newborn screening assay available currently.

(00:40:39):

Creatine transport deficiency, we do not have an efficient treatment unfortunately, and we don't have a newborn screening test that is reliable. But this is what on GAMT, if untreated a child, for example here, this girl, she's 14 months old and has GAMT deficiency, so the same severe disease that you saw at the beginning. If we treat, and we treated her from week three of life and she has had more and more development at that age. That continued as you can see. She is completely healthy looking and so that is accomplishable nowadays. So thank you very much for your attention and I will give back to the moderator. Thank you.

Heidi Wallis (00:41:40):

Thank you very much Dr. Schultze. I'd now like to welcome our moderator for today's meeting, Larry Bauer, who has been working with us over the past several months and he's helped us plan this meeting. Larry has worked for many years as a champion for the patient voice. He worked at the Cleveland Clinic Foundation and the National Institutes of Health before joining the FDA where he was a regulatory scientist in the Cedar Rare Diseases program.

(00:42:09):

He was at the FDA when the patient focused drug development initiative started and participated in some of the early meetings with patient advocacy organizations. Now in private practice, Larry continues to work with many patient organizations to ensure their community's voices are heard by decision makers. So thank you, Larry for helping us make our voices heard today. Larry and his colleague James Valentine have been involved in helping plan and moderate over 71 externally led PFDD meetings. So we're in good hands with Larry. And now over to you Larry.

Larry Bauer, RN, MA (00:42:50):

Thank you for that kind introduction and the opening comments. Heidi, good morning and welcome everyone. Heidi and I are coming to you live from the Washington DC metro area, which is not far from the US Food and Drug Administration headquarters. So now that we've heard a clinical overview from Dr. Schultze, we turn to the core of today's meeting, which is to hear from and learn from all of you individuals living with CCDS as well as their direct caregivers about the experiences of people living with CCDS.

(00:43:26):

The unmet medical need of creatine deficiencies is great, even overwhelming at times. Today is our opportunity to share your stories directly with the FDA, researchers, industry and other stakeholders to explain and share the many ways that CCDS impacts your daily lives. Patient-focused drug development, it's a more systematic way of gathering patient perspectives on their condition and on available treatments.

(00:43:58):

As we heard earlier from FDA's Dr. Chehowah, your input will help increase the FDA's understanding of CCDS from the patient and caregiver perspective and will help inform drug development and review. This is truly a unique opportunity for your rare disease, especially since there are over 7,000 known rare diseases. So while FDA has held many of its own PFDD meetings, CCDS, the ELPFDD meeting today marks the approximately 72nd externally led patient focused drug development meeting.

(00:44:38):

With thousands of known conditions, this is a unique and important opportunity for this community. Today's meeting is interactive, so let me tell you a bit about what will be asking of you and how today's meeting will be organized. In our morning session, we'll be exploring the patient and caregiver experience with living with CCDS and its impact on your daily lives.

(00:45:03):

In our second session after our lunch break, we'll bring everyone back together to explore the various approaches to treatment, including experiences in clinical trials. We will also be asking you about your preferences for future treatments. So what will our discussions look like? Well today we'll be using three different methods to engage with your community.

(00:45:26):

First, we'll be hearing from two panels of caregivers and patients with CCDS and these panelists will set a good foundation for our following discussion. The panelists that you'll see were chosen to try and reflect a range of experience with CCDS and the various subtypes of CCDS. Secondly, we will broaden the input through the use of polling questions. Patients and caregivers only will use their cell phones or laptops to respond to the polling questions. We will provide you instructions when it comes time for the polling

questions, but you can go ahead and get on the system now as once you are on, you'll be able to stay on throughout the entire day.

(00:46:11):

So if you take out your cell phone or open up a search tab on your computer, go to PollEV.com/CCDS. Again, feel free to go there now. It's PollEV, so P-O-L-L-E-V dot C-O-M forward slash CCDS and we'll get to some polling questions very soon. These polling questions are an opportunity to hear from everyone with CCDS in attendance and your feedback will aid in our discussion that follows.

(00:46:46):

And finally, we'll have a facilitated audience discussion with all patients and caregivers that are attending. The discussion will build on what we learned from the panels and the live polling. As your moderator, I'll ask questions on various topics and invite you to call in on the telephone number that will be provided on your screen. When your call is answered, you will be put into a queue or a waiting room until we can join with you live. So please be patient when you call in. You will still be able to listen to the meeting while you're waiting to be talked to live.

(00:47:22):

Also, we want to remind you to please state just your first name, where you're calling from, and what type of CCDS you or your loved one has before you begin to speak. There's also an opportunity to email written comments today as well as for 30 days after the meeting. And all of today's input and written input will be summarized into something called the Voice of the Patient Report, which will be written within a few months after the meeting and will be provided to the FDA and available for sponsors developing new therapies to treat CCDS. This is a report that will be in the public domain and anyone can access it and read it.

(00:48:04):

So to begin, let's have a few ground rules for the meeting. We encourage individuals living with CCDS as well as their caregivers to contribute to the dialogue via polling, phone and written comments. But I do have to say it is limited only to individuals with CCDS and their family members and other direct caregivers. People like the FDA, drug developers and clinicians are here only to listen and learn.

(00:48:33):

Let's remember that the views expressed today are inherently personal, and the discussion may get emotional, so please, respect for one another is paramount. To that end, please try and be focused and concise in your comments so we can hear from as many voices as possible. So I think to begin as a next step, why don't we go to our first demographic polling question. Once again, if you can take out your phone or your laptop and go to P-O-L-L-E-V.com/CCDS.

(00:49:09):

I hope that once you do that, you'll be able to see the potential responses and click on the one that you choose. I know in some families you have more than one child with a CCDS, so I ask that if it's only one person responding, please choose one of those children and make all the responses according to that child. If you have two children and maybe there's two family members or two caregivers, each one of you take one child and respond for that child.

(00:49:39):

So the first question that we have today is are you someone living with CCDS or a caregiver of someone with CCDS? You'll see that our responses are coming in in real time. I want to remind people that these

are not actual numbers, but they're percentages of the responses that are coming in, I think as we probably expected, 94%, most of the people are people that are caregivers for someone living with CCDS.

(00:50:12):

If we could move to polling question two. So this question is where do you currently reside? We have the US Eastern Time Zone, central time, mountain time, Pacific time. E is Alaska time, F is Hawaii. G is for those of you in Europe, H is for the Middle East, I is Asia or Africa, J Australia, K Canada, L Mexico or South America and M is other.

(00:50:50):

So it looks like we have people participating from not only all over the United States but all over the world. We have a large number of people in the central time zone, which is a little different. We have good representation from the Eastern Time Zone, the Pacific Time Zone, and a good number of people from Europe and even several folks from Asia or Africa and Canada.

(00:51:21):

If we could move to the third question. So are you or your loved one with CCDS, this is about gender, so female B is male, C non-binary, D prefer not to identify, and E is other. So the responses are coming in and it looks like we're about three quarters male and one quarter female. Is that what you would've expected, Heidi?

Heidi Wallis (00:51:58):

That's about right. Yeah,

Larry Bauer, RN, MA (00:52:00):

About right. Okay.

Heidi Wallis (00:52:00):

Maybe a little more female.

Larry Bauer, RN, MA (00:52:02):

Little more female. Okay, great. Okay, if we could move on to question number four, how old is the person with CCDS? So A is zero to five years of age, B six to 10 C 11 to 18 years of age, D 19 to 30, E 31 to 50, F 51 to 70 and G 71 years of age. And it looks like we have a large number of youngsters, about 35% in the earliest age group. About a third, third, third for the three youngest age groups and not too many folks over the age of 30. So that was unexpected. I didn't realize that.

(00:53:07):

Okay, if we could move to question five. Now, what type of CCDs do you or your loved one have or had? If we go back to Dr. Schultze's talk just a little bit ago, we remember that there are three main types of CCDSs. AGAT is the rarest with only 20 patients perhaps identified so it's not surprising that we're not seeing much activity there. We're seeing for the creatine transport disorders in the 80 percents and for GAMT deficiency 18%. There, actually now we are seeing that we've got someone participating with AGAT which I'm glad to see that we have that representation here. It's looking like 80%, we have a large representation from the CTD community. Okay, well thank you everyone. Like I said, please keep the poll

everywhere, app opened on your phone. We will be doing some more polling questions later in this session. Now I'd like to shift gears a little bit and talk about the discussion questions that we might be covering this morning.

(00:54:24):

As I said, the main topics for the morning are what are the symptoms of CCDS as well as what are the impacts of CCDS? So some of the questions that we'll be posing are, number one, of all the symptoms and health effects of CCDS, which one to three symptoms have the most significant impact on you or your loved one's life? Number two is how does CCDS affect you or your loved one on best and on worst days? And then maybe describe your best and your worst days.

(00:54:56):

Number three, how has you or your loved one's symptoms changed over time .and how has the ability to cope with the symptoms changed over time? Are there specific activities that are important to you or your loved one that you cannot do at all or as fully as you would like because of CCDS? What do you fear most as you or your loved one gets older? What worries you the most about you or your loved one's condition? So when we get to the open discussion, these are some of the things we'll be talking about.

(00:55:26):

I now would like to welcome the panelists that we have today. I said we actually have six people that will be presenting statements that they have worked on preparing. So now I would like to welcome Whitney, Kimberly, James, Jenny, Jerry, and Glenda.

Whitnie Strauss (00:55:47):

Hi, my name is Whitney and I am the parent of Reid, a 12-year-old with creatine transporter deficiency. As a parent of a nonverbal child with a severe intellectual disability and significant behavioral challenges, I learned quickly that armor was going to be a necessary component to our survival.

(00:56:07):

Reid entered this world as a colicky baby who rapidly dropped his birth weight due to difficulties with latching and completing feeds without assistance. From un-swaddling to rubbing ice cubes on his feet, these early weeks revolved around doing whatever it took to get our lethargic baby to eat. I was gifted then what I still believe was a lifesaving device in the form of a breast pump and completed newborn feeds by pumping breast milk into a bottle. Then with my hands, I manually expressed drops of milk into reed's mouth. By the time one feed ended, it was time for the next to begin.

(00:56:47):

This was the first time I put on armor and prepared myself for the battles to come. Feeding struggles and projectile vomiting became a way of life for us and a constant source of anxiety. Frequent car vomiting led to three car seats for Reid, one in use, one on reserve, and one was always in the wash. Reid was thin and battled to make up ground on the growth chart.

(00:57:15):

Pediatric visits were a weekly routine as we tried to explain Reid's feeding difficulties and GI issues, missed milestones, reoccurring ear and sinus infections and speech delays. By the time Reid was 15 months old, he had been on a dozen courses of antibiotics and was enrolled in twice a week PT, OT, and speech therapies. As Reid approached 20 months, cognitive impairments were becoming noticeable when he couldn't motor plan or pencil grasp or attempt to walk.

(00:57:50):

Equipped with only a weak failure to thrive diagnosis, we began to search for an explanation. Over the next year, we pounded the pavement with visits to gastroenterology, neurology, ear, nose, and throat, ophthalmology and allergy and immunology. Reid had an MRI, a tonsillectomy, adenoidectomy, got fitted for orthotics to help support walking, worked his therapies and gave more blood than most ever will.

(00:58:22):

In the fall of 2012, we'd finally found what we had been searching for and got the best worse news of our lives. We now knew what we were fighting, but Reid's genetic defect didn't have a treatment. We took this found knowledge and applied it toward managing Reid's symptoms, which now we're not only impacting Reid but our entire family. By now, we were all wearing armor. As G-tube feedings began and an epilepsy diagnosis emerged a thick skin also formed.

(00:58:56):

Ambulances in the driveway for grand mal seizures were normal. And, "Hold on just a second. Mom has to help Reid right now" became my mantra. My husband took a job closer to home after the night life flight landed in the front yard for the seizure that lasted over two hours. I'll never forget the shade of blue my baby was that night, but we got stronger.

(00:59:22):

Reid's gap in development compared with his peers was getting wider and lack of speech led to explosive tantrums, which in turn led to property destruction and self-injury. Constant biting on his arms and legs was leading to daily wound care and we needed more protection. So we put up walls and became immune to things like public stairs, broken bar stools, flying objects, refusal to wear clothing, breath holding spells and tiptoeing around triggers like loud noises that would lead to a physical attack on whoever was in arm's reach.

(00:59:58):

We'd do hard things like go to the grocery store. Well, Reid would scream drawing unwanted attention. We wouldn't cry when school sent emails announcing field trips and spelling bees and talent shows that were all light years beyond his reach. Reed's behaviors and seizure management were constant and ranged from ABA to supplements, to antipsychotics.

(01:00:23):

Public outings and finding respite care became nearly impossible. We lived within our walls and we trudged on. Simple tasks like holding a cup or stacking blocks took years to master, so the little wins like signing for help or pulling up his pants became the big wins for Reid. Our army rallied behind him and sacrificed. Doing things like going to the beach on vacation, the sand was just too scary. Eating out, sitting at a table was too hard. Having a mom in the stands at a baseball game, there were too many people, and so much more.

(01:01:01):

Also, Reid could find peace in our busy sensory filled world. When Reid was 11 years old, our family faced our hardest battle yet. Puberty was setting in. Aggressive behaviors were happening more often than not, and we needed reinforcement. We made the decision to move Reid to the Bayes Achievement Center, a residential school trained in behavioral management. Reid currently lives at Bayes and focuses on his behavioral, social, and functional goals like toileting, using utensils and self-care. Reid will never

live independently, but at Bayes he works to master those skills that he needs to come back home to us. We look forward when that day comes and maybe then we can begin to shed some armor.

Kimberly Morris (01:01:52):

My name is Kimberly and my sweet daughter Allison, age 22, is diagnosed with creatine transport efficiency or CTD. She's our first born and was an uneventful pregnancy. It was a fast natural birth and she appeared healthy and wonderful and has kept us on our toes ever since. At first, she seemed like a typical infant, but baby Allison had some difficulty latching, a rocky colic phase, but that didn't seem too unusual.

(01:02:22):

Soon after age one, we noticed delays in speech and some of the challenges with usual milestones. It was during elementary school that we went to Mayo Clinic and with further medical advancements in testing, we learned of Allison's diagnosis at the age of age 10. It was bittersweet. Knowing the label, but no cure and no proven treatment to try with uncertainty in their impact. We were told she was one of the first girls diagnosed in the world as primarily boys were tested and identified.

(01:02:56):

The experts suspected that there were many undiagnosed children, and in the years since then, we've found that to be very true. Many times I've received stairs as I've taken Allison to the store and she's had an outburst or a meltdown. It's the reason my husband or I try to run errands alone and others stay home with Allie. She doesn't know a stranger, so will hug people she doesn't know and maybe even try and give them sugars, which is her papa's term for a kiss.

(01:03:25):

That can lead to some awkward interactions. It also makes her vulnerable to strangers who have scary intentions. Allison has zero safety awareness and we need to keep close tabs on her whereabouts so she doesn't wander off or get injured. She can be impulsive and take a french fry from someone's plate as we walked by their table at a restaurant. Toilet training was long, hard, and messy. So is having female menstrual cycle monthly with the mental capacity of a toddler, but she's living it with support. Bras are tricky. Overall, it's just hard to-

PART 2 OF 10 ENDS [01:04:04]

Kimberly Morris (01:04:03):

Bras are tricky. Overall, it's just hard to be a girl with CTD. Allison has endured many challenges. I can only imagine what she wants to tell us if she could get the words out. I wish she could communicate when she has pain and where it hurts. I know she's missed out on sleepovers, driving, going to college like her sister, as well as texting with friends and living on her own. She needs constant supervision. That's a reality. Our family has experienced exclusion and isolation. There are places we would like to visit that we avoid for Allison's safety or we take her sister and we leave Allison with her grandparents. I wish we could take family bike rides and trust Allison to walk the dogs without us holding onto their leashes. It's uncomfortable to admit all this. Our life is not all giggles and sugars. More often than not, we're in survival mode, sleep deprived, a hot mess. Allison has taught us to be patient and calmer and that laughter is a really good medicine. There is no one template for life. She's inspired others with her infectious laugh and warm caring personality and her incredible manners.

(01:05:19):

In summary, the first 22 years have been phases of hard. The first 15 years, her behaviors and troubles seemed more intense. Then things leveled off for we got on a routine and now things seem to be changing again. As Allison becomes an adult, we don't know where her future holds. I've long worried she'd be injured due to her lack of safety awareness. I also wonder what CTD does long term. I worry if something happened to us that she would be in good, safe, loving hands and not a burden to anyone.

(01:05:54):

Just recently, we've noticed her speech is not as clear and she's not saying as many words. Despite weekly physical therapy and Horst therapy, efforts to stretch at home, her body is becoming more stiff and she's having complications walking and moving. Next month she's scheduled for her first surgery in hopes to help.

(01:06:16):

I know other 22 year olds have their whole lives ahead of them and exciting dreams and goals. I also continue to have goals for Allison, but I'm not naive to think that they might be unattainable. There are a lot of unknowns ahead so we don't make too many plans. We continue to live day by day.

James Mann (01:06:39):

Hi, I'm James Mann, parent to Freddie, who is a six-year old boy living with creatine transporter deficiency in London, England. Freddy was first diagnosed with CTD age two at a time where we were desperately seeking answers to why his development was delayed. We distressingly sought a diagnosis from a set of symptoms that when combined did not make any sense to doctors nor fit the pattern of any more common condition. He had terrifying breath holding episodes from age 10 months where when upset he would lose consciousness, his lips turning blue, his body rigid, then limp, and in being totally unresponsive for a period of around 10 to 15 seconds. He also had issues with his vision, a squint in his eye that reduced his ability to perceive depth, an inverted chest with pectus excavatum, along with him also missing all of his developmental milestones.

(01:07:41):

Given the wide variety of symptoms and severities patients with CTD exhibit in literature and that they didn't align with Freddy's, CTD was not something that doctors were expecting or had even shortlisted. And as a result, we needed to subject him to ever increasingly invasive tests to get to the root problem.

(01:08:04):

Freddy's breath holding episodes seem to be triggered by often fairly minor upsets, so we have continually tried to limit opportunities for Freddy to get upset, ultimately reducing the risks we allow him to take when playing, et cetera, and increasing how we are, likely further hindering his development and ability for him and as his parents to live a wholesome life.

(01:08:29):

Freddie does not naturally show curiosity and interest in the world and objects around him and is enabled to concentrate on tasks for any meaningful period. Given CTD impacted both his mental and physical development, Freddy doesn't possess the mental capacity or physical strength to ever truly play and will often drift away or become frustrated at his predicament. We know that he is able to learn and is able to acquire new skills, albeit just at a far slower pace, often in an orthodox way and with very intensive input and attention required from us to teach and coach in everything that he does. Teaching him to walk, talk, and acquire general skills needed for daily life. He currently operates in each of these

at a level far below his chronological age, which places a huge drain on our time, effectively becoming permanent one-on-one teachers to provide Freddy ways to improve his skills.

(01:09:34):

There is never any downtime or respite from the effort to try and keep Freddy safe both around the house and also when trying to provide him with well-rounded life experiences like visits to parks, shops, and restaurants that will help him develop. Such visits can often be incredibly difficult given Freddy's inability to stay close, follow commands and his total lack of awareness around safety. Socially, that has dramatically reduced our ability as a family to form friendships with others or to take part in things like play dates and psychologically is a permanent source of frustration for us, feeling that every moment should be dedicated to trying to bring Freddy on and the anxiety and worry of seeing him not develop. That comes often at the expense of investing meaningful time with his younger brother Oscar, who Freddy recently has begun to attack and to bite.

(01:10:33):

Freddy is prone to picking up sickness bugs. And once vomiting, will often continue to do so every 30 minutes for a period of up to 24 hours, becoming very lethargic and unresponsive. This requires intensive support and many visits to hospital to put him into medical supervision to stop the sickness cycles and to prevent him with such low body weight from becoming dehydrated or even critically ill.

(01:11:03):

Most recently, finding the right education setting has been a priority for us. And given how unique the set of symptoms and Freddy's challenges are, this has proven very difficult. We've got very used to him not being right for school after school. The level of intensive one-on-one attention he needs to remain engaged just can't be provided. Class sizes get too big and he gets overwhelmed, anxious, lost and starts to retreat. Other children get physically faster, stronger, and more boisterous than him such that he needs constant monitoring for safety and becomes totally isolated in the playground alone.

(01:11:44):

To accommodate the latest school, we've made our biggest adaption to our lives yet to give him the best chance of continuing to progress with formal learning, uprooting our lives from London to be closer to the school, hoping this could be the one. Making great sacrifices to chase the glimmer of hope we have of him leading an independent and sustainable life, but with very unnervingly no idea of what his future developmental outcome will be.

Jenny Lin (01:12:16):

My name is Jenny, and my 20-year old daughter Christina has arginine:glycine amidinotransferase deficiency or AGAT deficiency, one of the three disorders of cerebral creatine deficiency syndromes.

(01:12:29):

When Christina was born in 2002, she appeared to be a healthy, beautiful baby girl. But when she was around four months old, she really wasn't lifting her chest up while on her tummy as well as other babies her age. I also noticed that when I held her upright in my arms, I would often have to catch her and support her body so she wouldn't flip backwards. By six months old, she wasn't sitting up on her own. So I brought this up with our pediatrician who tried to reassure me and asked us to give her more tummy time so she could practice getting stronger. And so we tried that. But being a pediatrician myself and knowing that this could potentially be something more serious, it was hard for me to not worry.

(01:13:08):

By eight months old, she still couldn't sit up on her own, and even though she wasn't due for her routine checkup for another two months, I couldn't wait any longer and brought her back to our pediatrician. Our pediatrician still wasn't sure, but agreed we should look into it. And that's when our diagnostic journey began. What followed were a series of tests and referrals to many different specialists. By the time Christina saw the neurologist, she was already 10 months old and it became more obvious that not only was she missing her milestones, but she also wasn't gaining weight like other babies her age.

(01:13:40):

By 15 months old, she still wasn't crawling, pulling up to stand, actively babbling or feeding herself. I will never forget a party we attended at a park. While other toddlers ran around her having fun, Christina sat quietly on the grass. It was obvious she was less active, less engaging, and overall looked tired and disinterested. I overheard another parent whisper, "Is something wrong with Christina?" My heart sank and I went home that day and cried.

(01:14:11):

Despite all her tests, Christina was diagnosed with global developmental delay, hypotonia and failure to thrive. Words I knew as a pediatrician were often used by physicians when they just didn't know what was wrong. Christina eventually saw a metabolic geneticist. And as luck would have it, this specialist had just learned about a newly diagnosed group of disorders that involved creatine synthesis and transport. She wondered if Christina could be deficient in creatine. After even more tests, we were all stunned to find out that Christina had AGAT deficiency.

(01:14:47):

After months of not knowing what was wrong with Christina, you would think there would be a sense of relief for having a diagnosis because when you have a diagnosis, then you usually know what to do or at least know what to expect. But this was far from the truth for Christina. Instead, Christina's diagnosis was so new and rare that it created more questions than there were answers. We felt very much alone and scared. No one could tell us what Christina's future would be like. And although we did read about the few children reported in the literature who had AGAT deficiency, everything we read made us worry even more.

(01:15:22):

What we had read was that despite treatment with creatine, children with AGAT deficiency still had global developmental delay, severe language impairment, behavioral problems, seizures, muscle weakness, and low weight. Her metabolic geneticists however remained hopeful. These children were all diagnosed and treated much later in life, age four or later. She thought that perhaps early diagnosis and treatment was the key and hopefully Christina was diagnosed early enough that her treatment could make a difference.

(01:15:54):

At the time of Christina's diagnosis, she was only 16 months old. She was immediately started on creatine monohydrate supplements. We couldn't believe that within two weeks of starting the creatine therapy, we started noticing improvement in her activity, interaction and even her weight. Christina's developmental skills had also reached a plateau for months prior to her diagnosis. But after starting creatine, her motor skills improved dramatically and she started to walk shortly afterwards. But we knew that there were still a lot of uncertainty ahead. She continued to be followed very closely by her metabolic geneticist, neurologist, nephrologist, and developmental specialist, and she went to weekly physical therapy, occupational therapy and speech therapy.

(01:16:38):

As she continued to improve, she stopped receiving these extra services and each of her specialists started seeing her less. Christina was doing so well that visits to her specialist became an annual report of what Christina could do instead of what she couldn't do. And growing up, she did just about everything from ballet to playing the violin to now attending college, all while taking her creatine supplements multiple times a day. She continues to be busy, but more importantly, she is healthy. And here is Christina today.

Christina Lin (01:17:11):

Hi mom. Thanks for sharing my story with everyone. My hope is that other children with my disorder can receive early diagnosis and treatment so they too can have a chance at a healthy life.

Jerry Robinson (01:17:28):

We are the Robinsons and we are lottery winners. Well, not the kind of lottery that everyone hopes to win, not the kind that allows your financial burdens to be lessened, debts to be eliminated or obstacles to be removed. Nope, quite the opposite. We won a genetic lottery, similar odds of occurrence, I guess.

(01:17:49):

My name's Jerry Robinson, my wife Beth and I have three children. Our oldest, a boy, Benjamin, and youngest, a girl, Celia, were diagnosed with GAMT deficiency. While they will forever be tied together, their lives couldn't be more different. They were diagnosed on the same day and began treatment at the same time, but are four years apart in age and are following radically different paths because of the time of their lives that treatment began.

(01:18:18):

Benny came first, born in 2004. Early concerns came quickly. He was a very fussy baby, did not show a lot of interest in toys or movement, didn't mimic or make purposeful sounds, and was way late on all of his major developmental milestones. Most significantly, just before his third birthday, we noted that he was having seizure-like episodes which were confirmed by neurology. He was having a lot of seizures that interrupted his life constantly. He was treated with anti-epileptic or cocktails of them with mild positive results. Void a big diagnosis that would inform different treatment. We settled into a life of treating his epilepsy and getting him as many therapies as possible to help his development. Celia, our third child, arrived in 2008. Early concerns looked just like Benny. She was fussy and struggled with feeding. Most impactful were her failure to thrive and severe hypotonia. We found a new team of doctors and revisited genetics. When Celia was 13 months old, Benny was almost six, we received test result that would change our lives forever. Confirmed guanidinoacetate methyltransferase deficiency. Starting the treatment plan at 14 months old, Celia showed amazing progress. With continued therapeutic interventions, she had 10 months of developmental progress in her first five months of treatment. Crawled, walked and started talking. When she was around three, she was starting to refuse the formula and supplements and we opted for a G-tube placement to administer the medicines and ensure her continued recovery. She began preschool with a slight speech delay, which she received some therapy for. But by the time kindergarten rolled around, she was without delay and progressing normally. She's now in 8th grade, an honor student and a competitive dancer. She can have a normal life and do whatever she wants, although the medicines will have to be present throughout her life.

(01:20:18):

The challenges she faces now are mostly social. On her best days, she's a typical kid and is placing high in difficult dance competitions. On her worst days, she's angry and frustrated by having to take medicine three times a day through a G-tube when she just wants to be like everyone else. She's very private about her disorder and especially about her port. She's excused from class once a day to go to the nurse and take her meds, which she administers herself. The three times daily requirement is also an issue when spending time with friends at sleepovers or travel for dance competitions where she has to build in breaks or schedule when she have to get her next dose. In dance, the restrictive clothing irritates the port site and she ask for accommodations during costuming to make sure her port is covered or not obvious.

(01:21:08):

While Celia is proof that early diagnosis can lead to great things, Benny is a highlight of how devastating the disorder can be in the absence of early intervention. Now 18, he has a significant intellectual disability, severe motor planning difficulty, and is non-verbal. He's always taken his medications orally, all administered by us at home, further increasing his dependence on us. He's never said mom or dad in his own voice, although he does use an assistive technology device, which is his voice. He spent his years in school segregated in life skills programs with integrated therapy sessions. The biggest advantage of treatment for Benny was that he was able to come off seizure medications completely and went years without a seizure.

(01:21:54):

But one of our greatest heartaches is that Benny missed a chance to be more. While he should have had the opportunity to play all the sports he enjoys watching now and develop peer relationships in school, he instead participates in Special Olympics and spends most of his time with family. Benny will never live independently. He struggles with self-care and social awareness that significantly limits his ability to function safely in society. He cannot bathe or dress himself or prepare his own meals.

(01:22:24):

The disorder shows up in every aspect of our lives. Our best days, we appreciate health and how much worse it could have been without diagnosis or when the disorder just operates quietly in the background. Our worst days are filled with angst and anger and why us over the constant demands of the treatment when we spill powder or formula or have to skip out on an amazing opportunity because it's too cumbersome to manage with all of our baggage. We lament what could have been for Benny and worry about his future without us.

Glenda Corvera (01:23:00):

Hello, my name is Glenda. I'm Carly Hancock's mother. Carly was diagnosed with GAMT when she was eight years old, and she's now 23. Carly has a twin. Her twin brother doesn't have GAMT. She started having symptoms in utero. She did not move as much as the doctor would've liked. We spent a lot of time having tests to monitor her activity. She was delivered via C-section due to her being breached at 37 weeks followed by short NICU stay due to complications with temperature control after birth.

(01:23:33):

I started noticing she was not developing as her brother was when she was a couple of months old. He would hold his head up or try and she did not even try. She was not sitting up at six months old or meeting any developmental milestones. She started seeing a neurologist at 12 months. He diagnosed her with a developmental delay.

(01:23:55):

Carly was diagnosed with a developmental delay, cerebral palsy, autism, non-verbal and failure to thrive by five years old. At five years old, she started having tonic-clonic seizures. This was when our life changed. After being diagnosed with a seizure disorder, she had an EEG, which showed she was in a constant seizure state. Her brainwave activity was everywhere. Her neurologist stated he had never seen anything like it. I was not aware she was having them until she started having tonic-clonic and myoclonic seizures. She would have tonic-clonic seizures randomly and would last five to 10 minutes at a time and be postictal for an hour or more. She would have them a few times a month at first. Then with medication adjustments, it would get better for a while before the medications would not be as effective or would have to change to the side effects. She would be very combative and would pinch and bite others and herself. She would pull her hair out and knot it. It was an exceedingly challenging time. We tried different medications for mood, but they made it worse. She was always struggling.

(01:25:09):

Carly then went through genetic testing with a geneticist who believed there was an underlying cause for all her symptoms, but he was unable to diagnose it. After about three more years of adjusting medications, Carly was not getting any better. She was not gaining weight or improving cognitively. Carly was considered to be 18 to 12 months cognitively and was total care. She was having more frequent seizures. I decided to bring her to a new pediatric neurologist who performed a neuropsych exam. He stated she had an IQ of maybe 20. He suggested we go to Houston if she was to continue to deteriorate.

(01:25:50):

Carly at eight years old began having myoclonic seizure activity. I had to pull her from school and quit my job to be home with her. She was unable to stand without falling forward on her head. She no longer had an appetite. She was losing weight, weight she could not afford to lose. She was almost five foot tall and 86 pounds. She was no longer able to walk on her own due to falling forward onto her head. Her tonic-clonic seizure activity increased. I would stay up all night with her when she would have tonic-clonic seizures and need diazepam suppositories.

(01:26:29):

Carly's quality of life was almost nonexistent. Life was a struggle. I've said many times this was the worst time in our life. My daughter was dying before my eyes and I was helpless. I did not know what to do anymore so I made an appointment in Houston, and from there we started to get answers. We had an eight-day hospital stay and she received her diagnosis of GAMT. No one understood GAMT back then. The treatments were not clear. We then were discharged with an extremely strict low protein diet of eight grams a day and medication three times a day with formula twice a day. This was unbelievably hard. Carly did not want to eat low protein foods or take medications. It was a fight.

(01:27:18):

Carly will always be my baby. She will never have a so-called normal life. Her disease and late diagnosis has robbed her of that as her brothers have all their milestones, she has none. She will never graduate from school, marry, or be able to experience friendship. She will always be two to three cognitively and non-verbal. She'll never be able to perform her own activities of daily living. She will always have to rely on others for all aspects of care. Of course, I wish things were different, but they're not and they never will be.

Larry Bauer, RN, MA (01:28:00):

Thank you so much to our panelists that have shared their incredible stories, shared very personal stories. We appreciate it so much for giving us that opening into the topic of the morning session, which is disease symptoms and life impacts.

(01:28:19):

Now, to continue with the session, I would like it if we could go back to another polling question. So if everyone could please take out their phone or their laptop, and once again, go to pollev.com/ccds. pollev.com/ccds. So the first question we have this morning is, which of the following health concerns has the person with CCDS ever had? Please select all that apply. So if there's many, choose as many things as you think are appropriate. We have A, speech delay or no speech. B, developmental delay. C, intellectual disability. D, seizures. E, gross motor challenges such as walking, running, climbing. F, fine motor challenges like pencil grasp, using scissors or zipping. G, behavior issues like autistic-like behavior, self-injury, aggression, et cetera. H is focus and attention issues. I is GI problems such as constipation or vomiting. J is failure to thrive. K is movement disorders, which could include involuntary movements or tremors, and L is other.

(01:29:41):

So I see that people continue to input. I mean, just visually looking at this, one of the first things that I notice is how so many of these symptoms affect so many people with CCDS. So speech delay or no speech and developmental delay are slightly ahead, but we also see that intellectual disability and fine motor skills are getting a lot of responses as are behavior issues and issues related to focus and detention. A significant number of people are reporting seizures. And then we have GI problems, failure to thrive and movement disorders also being represented. We're also noting that we've got about 3% of the responses are saying others. So maybe when we get to our discussion section, we'll hear a little bit about what other is.

(01:30:39):

Okay, so let's move on to the second question on this topic. So now this is a list that's identical to the list that you had, but now this time we would like you to select the most troublesome health concerns that the person with CCDS ever had. So out of all those symptoms you identified in the first question, what are the top three health concerns that you think that you or your child has? Once again, if you're a parent with two children, please respond to these questions for one of your children. And maybe if there's someone else in the family that could key in the responses for the other child, that would be great.

(01:31:24):

So once again, we're seeing speech delay or no speech as the front runner at the top, with intellectual disability being one of the most troublesome health concerns. We're seeing seizures as being more impactful. Not as many people reported it on the first time, but for those that have seizures, it looks like those are having a strong impact. Developmental delay. And then behavior issues also as giving a significant number of responses like the autistic-like behavior, self-injury and aggression, which is we heard from some of our panelists. And then there are some people that have identified gross motor challenges, focus and attention, failure to thrive, GI problems and movement disorders all got some responses. And once again, there are some other things that maybe we don't have here that people think are their top health concerns.

(01:32:33):

So thank you everybody for those responses. We are now back in the studio and we are being joined by five different people. These are all caregivers of children living with CCDS. So we're joined by Celine, Carol, Rachel, Beth, and Trey. Welcome. Thank you so much for joining us. We're so happy to have you here with us in the studio.

(01:32:59):

So we just did those polling questions and one of the questions, the second one was about what are the top three symptoms that impact your child's life? I was wondering, Celine, would you be willing to talk a little bit about that?

Celine Wheaton (01:33:18):

Sure. Hi, my name is Celine. I'm speaking here from Southern California and I have a 16 year old boy, Matthew, with CTD. It was hard to choose which three are most impactful. I want to say that the top one for me was probably the lack of speech because without this speech, he cannot tell me where it hurts, he can't describe how he's feeling. He can only scream or grunt or cry or also laugh and giggle and smile. He's very expressive in other ways, but he can't specifically pinpoint any of the problems that he's having. For example, he's having some tremors we think at night, we weren't sure if these were seizures or if they were a side effect from some new medication that he was put on, or it was related to some GI problems, but he can't really say, "Oh, it's my stomach that's hurting me, mom. That's why I'm waking up at night all the time."

(01:34:42):

Second, I think I put intellectual disability, although I feel like it's hard to really pinpoint exactly where he falls on the spectrum because testing his intellect is difficult. And then, what was the other one? Oh, I put GI problems because right now it's very prevalent for him, although seizures come close in there because it's so scary. But yeah, that's what I'd say.

Larry Bauer, RN, MA (01:35:21):

Okay, thanks Celine. Before I go to the next Zoom caller, I want to remind everyone that you can also be phoning in comments. To telephone in a comment, dial 703-844-3231. Once again, the phone number is 703-844-3231. A little bit later we'll try to get to as many callers as possible.

(01:35:50):

Celine, I had one follow-up question for you. You mentioned it sounded like Matt has troubles with expressive speech. What about receptive? Like, when you ask him to do something, he is-

PART 3 OF 10 ENDS [01:36:04]

Larry Bauer, RN, MA (01:36:03):

... Receptive, like when you ask him to do something, he's given a direction, how's his receptive capabilities?

Celine Wheaton (01:36:10):

He pretty much understands a lot of what's going on. He laughs at appropriate times if he hears something funny or if I'm getting mad at his dad or something like that. But it's also built on routine, so it's hard to tell. So he knows if I say, "Oh here, take this remote and put it in the basket," he knows, "Oh,

it's time to turn off the TV and put it in the basket." But it's a routine that's been built up. So it's kind of hard to suss out what he's really understanding or if it's because it's built on routine.

Larry Bauer, RN, MA (01:36:55):

Okay. And have you seen any change in that symptom in his communication abilities over time or has it been consistency? You said he's 16 now. Has it been consistent since he was a young child?

Celine Wheaton (01:37:08):

Yeah, I mean he's never had words. He's only babbled a little bit when he was a baby, then lost that. I mean, he is expressive as far as emotions and some made up signs that he uses as well as a communication device. But the communication device, he'll use it when he wants to use it, mostly.

Larry Bauer, RN, MA (01:37:39):

Okay, thank you so much. Rachel, could I ask you the same question when you heard, what are some of the top three most impactful symptoms? What did you choose?

Rachel Cafferty (01:37:50):

Yes, my name is Rachel and I am from Minnesota. We have a 10-year-old boy with CTD, and I would say my three top concerns are probably the intellectual disability. I think that covers a lot of ground there. It impacts his speech, his attention and his behaviors. My second would probably be his speech. Like Celine said, it's hard for him to communicate his wants and needs. Gilbert does have quite a few words and can string probably three to four words together, but he's not always sure of what he's choosing. When you ask him a question, he'll often choose the last one versus what he really wants. And so we're constantly needing to rephrase things to make sure that what he is asking for is what he really wants. And then the behaviors, as he's gotten older and gotten stronger and I'm getting older and weaker, it makes that a little bit more difficult to handle him at times. He'll self harm himself, he'll bite, he's bitten me and his sister. And so I think some of those behaviors are becoming more of a trigger and harder to handle.

Larry Bauer, RN, MA (01:38:56):

Okay, thanks. And so can you tell us, you said that Gilbert has a few words. Can you tell us a little bit more how he uses those words or what kind of things does he express with that limited vocabulary that he has?

Rachel Cafferty (01:39:12):

Yeah, Gilbert is very, very inquisitive. So he always wants to know what people are doing. So that's a common question you get asked over and over and over again. He's able to communicate his basic needs. So if he's wet or hungry, he's able to ask for specific foods that he wants and places to go.

Larry Bauer, RN, MA (01:39:29):

Okay.

Rachel Cafferty (01:39:29):

It's just very limited. He's got a good vocabulary, but isn't able to string more than three to four words in a sentence and isn't always able to get across all of his emotions or feelings or desires that he wants.

Larry Bauer, RN, MA (01:39:42):

Okay. And do you feel like that his inability to communicate emotionally contributes to the behavior and the aggression?

Rachel Cafferty (01:39:50):

Yeah.

Larry Bauer, RN, MA (01:39:50):

Can you tell us about that?

Rachel Cafferty (01:39:51):

Yes. I feel like sometimes when he gets frustrated or irritated or even like Celine said, when he's in pain he's not able to pinpoint those. And so sometimes we see that, that come out in behaviors when he is not able to communicate effectively with us.

Larry Bauer, RN, MA (01:40:05):

And has Gilbert ever been injured? I'm always get when someone says that their child can't express when they're hurting or something. Has Gilbert ever had an injury and you didn't know what happened or what hurt?

Rachel Cafferty (01:40:18):

No, nothing like that, to that extent, not any injuries like that. So thank goodness.

Larry Bauer, RN, MA (01:40:25):

Okay. Thanks. What about... Let's see, Carol, would you like to respond to that about some of the top three?

Carole Chehowah (01:40:36):

Yes. Good morning all. I'm Carol. I live in Paris, France and I'm the mother of Elise, 32 years old, who was diagnosed with CTD when she was 16, and it was hard to pick up three key symptoms that are bothering her life, but I put ID, seizure and behavior and depending on the days, one can be worse than the other one. But like Celine and Rachel said, the behavior, of course, is linked to the ID and the difficulty of being understanding and to live with normal people. When you have an invisible disability, people expect your kid to be like the others, and they're not. In the case of Elise, she speaks quite well. So she has a lot of vocabulary. She repeats a lot, but she's able to say what she wants, what she doesn't want, and to express when she's frustrated although it doesn't avoid the behavior problem and she hurts herself.

(01:41:59):

She can, if you want to take her, she can hurt yourself too. She pull her hair, she run away in the street, she can break a window. She's quite unpredictable when she's bad. And on the contrary, she can be very, you say that, she's [inaudible 01:42:24] in daily life things, so it's a mix. It's a bit different, maybe, because she's a girl and the CTD doesn't express the same way. But clearly the behavior and the seizure that get worse as she's getting older. And that's a key problem for us and for her too.

Larry Bauer, RN, MA (01:42:50):

And can you tell us, Carol that, so Elise wasn't diagnosed till she was 16 years of age. What happened earlier? When was her first presentation of symptoms? Even though diagnosis didn't come till 16.

Carole Chehowah (01:43:07):

Okay. First when she was 18 months, then she was a bit different from the others, although she was the tallest, the more smiley girl, et cetera. But at this time, they thought it was maybe something related to the mom, to myself actually, how I raise her. And maybe there was some psychological problem. So from 16 years, we came from psychologist, psychiatrist, pediatrician back and forwards, and we just have a sense of guilt of what we have done wrong or not. When she turns 14, she was diagnosed as autistic. So that was the first time we heard about something different than myself being not the right mother. And then when she was 16, she was diagnosed with CTD finally. And so we can split our life in two, 16-year-old with no diagnosis and then 16 years with CTD diagnosis, and it changed our lives. Is cured or she has a treatment, but she's seen the right people, the right physicians, and now people would look at her differently and that's very important too.

Larry Bauer, RN, MA (01:44:31):

Yeah, it's interesting we heard from Dr. Schulze say that people living with CTD, that they can express all these different symptoms. And you mentioned that the seizures are getting worse. Can you tell us at what age Elise had the onset of seizures, and what's that pattern been like? Have they increased in number and severity? Have they remained the same?

Carole Chehowah (01:44:57):

Okay, so the first time she had seizures, but we didn't know what it was when she was around 10, 11 years old. And she was treated for the stomach because nobody knows about CTD or anything. So she was treated for something else. And when she was diagnosed at 16, the genetician told us that she might have epilepsy, and he describes different seizure type. And of course, I told him, "Oh, by the way, she has that, it's not very frequent, but it's, maybe, once a week or twice a week. And the intensity is different times to times." And after 20, 22 years old, it starts to be more and more and for the last two, three years, it's more intense and it has high dimension at the beginning, it's pharmaco resistance so it's hard to find a treatment. We recently changed the treatment and it's working a bit better. So we hope this time it's the right one and she will have less seizures.

Larry Bauer, RN, MA (01:46:12):

Okay, well, thank you, Carol. I see that we have a phone caller on the line. We have a caller named Brittany calling in from Minnesota with a child with CTD. Brittany, are you there?

Brittany (01:46:31):

Hi, yes. I'm here. Yep. My name is Brittany, I'm calling from Minnesota, and I have a three-year-old son with CTD. So I just want to say thank you so much for the opportunity to share some of our experiences as families and caregivers and some of us as patients. But I did want to share a little bit about the three things that are impacting our family aside from what has already been discussed and what is obviously a top couple of concerns for us as parents and those being speech delays and then seizures or intellectual disability. I think one thing that's been tricky for us, we have recently learned of the diagnosis. Our son

was 20 months old when he was diagnosed with CTD. It's a blessing and a curse as we all know, to have an answer but also not understand exactly what this means and what this will mean for his future.

(01:47:31):

I think the scariest thing, I was one of the people who put others in the comments for things that are impacted and that impact us in our day-to-day lives and that are just the most scary, are some of those things that are unknown to these conditions and that sneak up out of nowhere. So for my son, he has prolonged QT syndrome, which impacts his heart. We don't know what that means for him in the future, but he's unfortunately on a medicine for that.

(01:47:57):

And on top of that, he had a recent event of severe... He had a recent severe hypoglycemic events where he wouldn't wake up one morning because his blood sugars were so low and luckily we were able to get him the treatment he needed. But I think as a parent, the concern is beyond the things that we know about with this condition is things that we don't know about. And so if we can find some way to get help or treatment for our child, maybe some of these other things will also be some of these other things that are scary for us and that worry about... that make us worry about our child's future will also be mitigated.

Larry Bauer, RN, MA (01:48:41):

Correct.

Brittany (01:48:41):

So I just wanted to share that.

Larry Bauer, RN, MA (01:48:42):

Yeah, thanks Brittany. I have a question for you. We haven't heard about prolonged QT syndrome. How was that found out that your son had that? Did he present with symptoms? Was it on a routine screening? What happened?

Brittany (01:48:59):

Yeah, so I'm not going to tell the whole story, but when my son was first diagnosed, it was due to a tonic-clonic or the grand mal seizure. He had seven within 17 hours and we didn't quite know why. And so of course, they go through the gambit of what happened? Was he... They thought he may have gotten into some type of something poisonous substance or something, all the things that you're like, there's no way this is something that could happen. And they were trying to rule out several things potentially like a viral encephalopathy et cetera. And so they did so many tests, all the tests that I know all the parents and caregivers here know about lumbar puncture, multiple blood tests and MRI, et cetera to figure out what is the root cause of this.

(01:49:47):

And with that, they saw that it was prolonged, his heart rhythm was prolonged and they had a followup just to make sure, maybe, that was just an event that was happening in the hospital because of his current situation and now it was found to be prolonged at that point. And I'm glad it was found because we're able to have an extra seatbelt with the medicine he's on. But again, it's another thing on top of the big condition that we're already concerned about.

Larry Bauer, RN, MA (01:50:18):

And Brittany, did-

Brittany (01:50:19):

So that's how we found it.

Larry Bauer, RN, MA (01:50:21):

Okay. And I was just wondering, are the experts that your son is seeing, do they think that the prolonged QT and the hypoglycemia episode, do they think that these are CTD related?

Brittany (01:50:32):

So it's hard to say, and I feel like this is, I think it depends who you ask. So for us, I think that we've been given the answer of, "It could be, it could be related" and for us, we're like, it has to be, all these things are just coming out of nowhere, but there's one root cause where it's happening. So I think the most troublesome one was the blood glucose and the drop in his sugar level, which was completely off of our radar. Our son is fortunate to be a very good eater, but looking back, he had a stomach bug and there were some things that kind of led up to it that give us a better understanding of it. But I think in some of the conversations I've had with the community, there have been other instances of lower blood sugars and hyperglycemic events and I know that several other folks also have kids that have the prolonged QT.

Larry Bauer, RN, MA (01:51:35):

Okay, thank you. It's very interesting. I'd like to ask Heidi. Heidi, have we gotten any written comments coming in on this topic about symptoms?

Heidi Wallis (01:51:44):

Yes, we have a few comments, I think, would be great to share right now. Ashcon from Canada comments that our son has global developmental delay that affects his day-to-day activities. His understanding is like a two- to three-year-old kid with speech delay that doesn't allow him to communicate with others. He has fine and gross motor skill delays that limit his daily routines. He cannot focus and concentrate on a topic. He also suffers from different types of seizures with each one being as scary as the previous one. Next comment is from Thaluma in Brazil. She comments our little one, four years old son has a lot of energy, a lot of desire to learn, but his hyperactivity makes it difficult for him to learn. He still doesn't know how old he is. He wears diapers, he tries to communicate but fails, he can't speak. He has behavioral oscillations.

(01:52:51):

They can't take him out to lunch for example because he doesn't stay still for more than two minutes. And then lastly, I'll add one from a GAMT parent. This is Marie in Florida and she comments that her daughter went untreated for nine years and this has caused issues with her speech, severe learning delays, motor coordination and epilepsy and comments that, had this been on a newborn screen, they could have had a different start at life.

Larry Bauer, RN, MA (01:53:27):

Okay. Well thank you very much for those. I also see that we have, on the telephone, Regina from Oklahoma who has a child with CTD. Regina, are you there?

Regina Bogar (01:53:43):

Yes I am Larry. Thank you.

Larry Bauer, RN, MA (01:53:46):

Yeah, what would you like to share, Regina?

Regina Bogar (01:53:47):

I just wanted to piggyback a couple of your panelists and your previous caller, when we're talking about, I was also one of those that put other as one of our concerns and I'm going to piggyback the cardio and add pulmonary to that as well. I have two CTD patients. I have a daughter and a grandson who I am the caretaker of, and the grandson does have borderline prolonged QT. However, we have noticed with any and all illnesses he has pushed over that line and goes into the prolonged QT diagnosis. However, he does rebound once he's well and goes back down to just the prolonged QT status. You had asked about injuries on the panelist and I will say that our expressive, receptive language skills speaks into that as far as my grandson, Caden did walk on a hip fracture that we did not know was fractured and the orthopedist believe that was a case for him for about a year. Unfortunately, that did happen during COVID where you're not in and out of doctor's offices. And when we see the patients, we care for these individuals day to day. Sometimes the abnormalities in their gait and in their hypertonia and hypotonia, we don't always see changes because they can be gradual and we're used to the unusual presentation of their gate. And for Caden, it happened to be on a virtual appointment where his pediatrician asked me, "So what else is going on with our little man?" And I just said, "Other than the little wiggle in his hiney, he's developed."

(01:55:20):

And she said, "What are you talking about?" And asked me to show her a video. And so we did, and she quickly said, "I'm sending you straight to get an x-ray." And so being unable to interpret pain, feel pain in the way that we would identify it and then to be able to express, "Hey, I'm not feeling well. Ouch, this hurts" can also lead to other comorbidities or prolonged diagnoses of other injuries and such. And so I just wanted to chime in and piggyback to that and show that, that can cause obviously you go into behavior issues with that, you are not feeling well, you're walking on pain, that can turn into agitation, oppression, anxiety. So then you start seeing the behavioral downfall of that, and it just all feeds into each other.

Larry Bauer, RN, MA (01:56:03):

Oh wow. Thanks, Regina. And your son was not, when he fractured his hip, he couldn't communicate in any... You didn't know for an entire year. Is that correct?

Regina Bogar (01:56:15):

Correct. It's my grandson.

Larry Bauer, RN, MA (01:56:16):

Oh, your grandson, got you.

Regina Bogar (01:56:17):

We did not know, and it actually wasn't a fall injury or an actual injury to it. He actually developed leg [inaudible 01:56:23], which is a whole another disorder in itself. But because basically the blood flow to the head of the hip bone stops and it begins to deteriorate, and as it deteriorates, it fractured. But he was unable to tell us that he was feeling uncomfortable or whether or not he could even feel that pain, we are still to this day unsure of, but based on the bone regrowth, whenever it heals itself, they believe that it had happened within a year's time and that he had been walking on it for a long period of time without anybody recognizing it, realizing it or him being able to communicate it or feel it.

Larry Bauer, RN, MA (01:57:00):

Wow. That must have been... what was that like to be his mom and to realize when that had happened?

Regina Bogar (01:57:08):

His mom felt bad because she didn't recognize it. I felt bad. We do live as a multi-generational caretakers, and all of us felt as a caregiver, it's our job to watch for those subtle signs. And this is where the emotional part comes in for us as families. When we don't know, we don't know. And I think that kind of piggybacks what the other caretaker just said. It's the fear of the unknown and not being able to recognize and realize what's happening inside their bodies to be able to help them in a timely fashion and give them the help that they deserve and need.

Larry Bauer, RN, MA (01:57:41):

Wow. Well thank you very much, Regina for calling in and sharing your story. We appreciate it. I'd like to get to Beth and Trey in just a minute. There are two panelists that we haven't heard from yet. Just a reminder to everyone if you'd like to call in with a comment, the number is 703-844-3231. But now I'd like to go to our next polling question. Polling question is related to symptoms and impacts.

(01:58:18):

So this question is what specific activities of daily life does the person with CCDS struggle with? And in this case, you can select the top three. The first one is communicating effectively. B is following complex instructions. C is learning at the same rate as their peers. D is self-regulation, impulse control under executive function. E is toileting and self-care behaviors. F, engaging in social interactions. G regulating emotions appropriately. H is completing daily tasks independently. I is adequate health to attend school or work. So they're not having seizures, they're healthy enough to go to school or work. And J is other. And once again, please select your top three as we're beginning to hear consistently, communication and communicating effectively is a serious life impact for people living with CCDS. Toileting and self-care behaviors is also rising to the top, self-regulation and impulse control, issues with learning and completing daily tasks independently. And some people have chose following complex instructions, engaging in social interactions, regulating emotions appropriately. And it looks like maybe a couple people have chosen adequate health to attend school or work. But as the answers continue to come in, it's the communication one that continues to get the top percentage of responses and the toileting self-care behaviors. It's also, it's something we haven't heard totally about, but that's something that many people, it's actually the number two choice that people have is, one of the most impactful activities of daily life that the person struggles with. Okay. Well, thank you for your responses to this question. If we could go back to our Zoom panel. And Beth, so when we're talking about the challenges and struggles, what came to mind for you?

Beth Robinson (02:01:10):

Hi, Larry. Hi, Heidi. My name is Beth and I have three children. Two of them have GAMT. Our oldest, Benny, he is... he'll be 19 at the end of the week. And our youngest, Celia and she is 14. They have GAMT, and we are from Chicago, Illinois. So it's interesting you had just discussed this self-care issue because that's something we really struggle with, especially with our oldest. They were diagnosed together, however, they're four years apart. So Benny had suffered the consequences of GAMT for four years longer than Celia had. She was one at that time. So he is 18 now, soon to be 19. And self-care is one of our biggest struggles. We have to help him shower and dress himself, make all his meals for him. That's our biggest struggle for sure.

(02:02:22):

And finding someone to do that is extremely difficult. So that means that he's totally dependent on myself and my husband to do that. And looking into the future, finding someone who will be able to do that for our son is terrifying at the least. Nobody wants to leave a completely vulnerable child in their care in the hands of somebody else. And he also does not have any speech. Benny is also non-verbal. He uses a device to communicate so that further impacts his... how difficult it is to find care for him.

Larry Bauer, RN, MA (02:03:08):

Okay. And do you get outside care that comes into the home to help?

Beth Robinson (02:03:15):

Currently we do not have any outside care for Benny. We rely, it's just my husband and myself, and we have made it possible through our schedules to be home. I can only work a certain number of hours during the day, and I have to be there when he goes to school and immediately when he comes off the bus. So that really affects your life. I can't work outside of those hours. So it's just us right now and grandparents do help out, but they're getting older and Benny's getting bigger and stronger. So I'm not sure how viable that option is. He does have two sisters, but we don't want to put a lot of his care in their hands. So right now it's just us.

Larry Bauer, RN, MA (02:04:05):

Okay, thanks. And what about Celia, your daughter that's affected with GAMT? What are some of the greatest impacts on her activities?

Beth Robinson (02:04:15):

So Celia has made, its almost a full recovery, because she was diagnosed early and was able to begin treatment much quicker than Benny. So looking at Celia, you wouldn't know that she's dealing with anything like GAMT. So right now, her biggest issue is the medication administration, getting the supplements to her during the day and still being a normal teenager. She's an eighth grade now, she'll be going into high school and that's a very self-conscious time for kids. And she does have a G-tube and she's very private about it. But these medications are terrible. She takes all the powder supplements and she has a metabolic formula and these are extremely necessary for her to receive. And so we opted for the G-tube and right now it's just her making time out of her busy day of a normal teenager to stop what she's doing, get those medications through a very personal way through this G-tube and still maintaining her any type of normalcy.

Larry Bauer, RN, MA (02:05:25):

Okay. And how long has Celia had a G-tube?

Beth Robinson (02:05:31):

So that was put in when she was three years old.

Larry Bauer, RN, MA (02:05:34):

When she was three.

Beth Robinson (02:05:35):

She was diagnosed at about one and then it became clear that she was going to be, this was going to be a struggle for us. She became non-compliant and we knew looking at Benny, what happens when you don't have treatment. So it was pretty clear that we needed to act upon that and she doesn't want to have the G-tube, but these are very difficult medications and supplements to take. It's not a pretty little pill and it's not a sugary syrup. It's a constant struggle and these things are absolutely vital to her future, and they will be with her for the rest of her life. So she will be an adult still administering these things. And that's another issue, pretty soon she'll have to be able to do this by herself.

Larry Bauer, RN, MA (02:06:20):

Okay. And other than the G-tube and having to take the medicines, does Celia have any impacts? Is it like nothing really affects her? No?

Beth Robinson (02:06:31):

She does not. She is in a regular classroom in eighth grade. She gets straight A. She's in some honor classes, and she's a competitive dancer and you wouldn't know that she's dealing with any of this. And that's strictly because she was diagnosed early and began treatment as early as possible.

Larry Bauer, RN, MA (02:06:52):

Yeah. So I mean, from what you've described, the impacts on your two children's lives are it's been really two different stories, two complete stories, is that correct? Yeah. Okay. And Trey, what would you like to share on this about the life impacts?

Trey Wallis (02:07:12):

Sure. I'm Trey. I'm from Salt Lake City, Utah. I have two kids with GAMT deficiency. Samantha, who's my daughter is 19 and Louie, who is my son is 11. Very similar to Beth's experience, actually. Samantha was diagnosed at around five and has sort of lifelong developmental delays and speech challenges and seizures and all of those things. And Louie was diagnosed pretty much at birth and does not have those effects, but still needs to obviously take supplements and very similar experiences to what Beth is talking about.

Larry Bauer, RN, MA (02:07:57):

Okay. And Trey, does Louie have a G-tube? I'm just curious, do either of your children have G-tube?

PART 4 OF 10 ENDS [02:08:04]

Larry Bauer, RN, MA (02:08:03):

Does Louie have a G-tube? I'm just curious, do either of your children have G-tubes?

Trey Wallis (02:08:05):

No, neither have G-tubes.

Larry Bauer, RN, MA (02:08:08):

Okay. And so what are the greatest activities like for Samantha? What is it? How is this that GAMT is affecting her? What is it that she cannot do, or what's the biggest impact? When you think about a child, I'm sure you guys have worked with Samantha as much as possible to optimize everything for her, but compared to the development of different teenagers, how's Samantha's life been impacted?

Trey Wallis (02:08:38):

Yeah, I would say the biggest impact is the seizures. In fact, seizures were what initially led to this diagnosis. So when she was probably three or four, we noticed a lot of non-convulsive absence seizures, where she would just get an eye roll and not really pay attention anything. Those have progressed into convulsive grand mal seizures, and that really impacts almost anything you could even try to do to get someone like her to do anything independently because you never know what will happen. And as a lot of us have found out it's not necessarily the seizure activity that causes damage. It's the falling and losing normal consciousness that causes all the problems. And we've had situations like that. We've had broken arms and collarbones and things just from having a seizure and falling awkwardly, and those things will happen. That's a really, really big impact. The frequency of those are anywhere from once a week to... I mean, we're probably lucky if we get three weeks in between seizures, so it's fairly frequent. So that's probably the biggest impact. The second would be just communication and intellectual disability.

Larry Bauer, RN, MA (02:09:57):

And what's the impact been on Samantha's school life? School is such a big part of kids' lives. What's Samantha's journey been like with school? What have the impacts of GAMT been on school and development?

Trey Wallis (02:10:12):

We made an attempt around kindergarten. We held her back for a year, so she went when she was six. We made an attempt to try and mainstream her, and it just became too difficult. She needed to go to a special program. We were very fortunate in that we live in a school district that has a fairly good SPED program that we could put her in, but now, she's out of the public school system, and she's basically in specialized programs at this point.

Larry Bauer, RN, MA (02:10:43):

Let's see. She's 15 now. So do they have the same grades?

Trey Wallis (02:10:47):

She's actually 19.

Larry Bauer, RN, MA (02:10:48):

Oh, she's 19 now. So is she close to finishing school or...?

Trey Wallis (02:10:52):

Yeah, she's done with public school. Okay. So she's now in just intellectual disabilities program daily.

Larry Bauer, RN, MA (02:10:59):

Okay. And what about the impacts on her social life?

Trey Wallis (02:11:05):

Yeah, I mean, it's nonexistent, right? I mean, her social life consists of her family and relatives and maybe a few friends at her school, but when you can't really communicate in a normal way, that becomes a challenge. So she wants to be social. You can tell she has a desire to be with other kids, and she's happier with other people, but she doesn't want to be with other disabled kids. That's the other thing we've noticed. She wants to be with people that are... For lack of a better word, they're normal, and that's who she wants to hang out with. But that interaction is obviously limited because of her ability to both process and produce good speech.

Larry Bauer, RN, MA (02:11:49):

Okay. Tell us about your communication with Samantha. How do you communicate with her? How do you try to understand what she wants, what she needs?

Trey Wallis (02:12:00):

Yeah. Slowly and positively is probably the best approach. I think that Samantha, in particular, is pretty sensitive to emotions that she picks up. And so she'll very quickly tell if you're upset or if you're not feeling good or whatever, and then she tends to reflect that back to you from an emotional standpoint. So it needs to be simple. It has to be very simplified. You can't give her a list of tasks, for example. You can't say, "Put this away. Then go get this glass out. Then do this." You have to be very specific, and it's a single task, and it has to be fairly simple. Anything complicated or that requires anything more than maybe one step, she won't try, but she won't be able to really figure that out.

Larry Bauer, RN, MA (02:12:49):

Okay. And has her communication ability changed over time from the time she was little to now?

Trey Wallis (02:12:58):

Yeah, she almost had no vocabulary when she was first diagnosed around five years old. And then, she can string together very simple sentences. It's their stutters, and there are other challenges and understanding them. Her pronunciation's not great, but you can put things together. But similar to some of the other comments due to the lack of vocabulary, and the challenge is she does have a hard time explaining where something hurts or what exactly. I mean, she can say, I don't feel good. But then if you try to diagnose that any more of, "Is it your stomach? Is it your head?" You're not really getting anything out of that. She's just like, "I don't know."

Larry Bauer, RN, MA (02:13:39):

Boy, that sounds incredibly challenging.

Trey Wallis (02:13:41):

Yeah.

Larry Bauer, RN, MA (02:13:41):

Okay. Well, thank you, Trey. I'd like to shift. I think we have someone on the telephone. It looks like we have Celeste from North Carolina who's has a family member with CTD. Celeste, are you there?

Celeste (02:13:58):

Yes. Hey, Larry. Hey, Heidi.

Larry Bauer, RN, MA (02:13:59):

Hi, Celeste.

Celeste (02:14:01):

Hi.

Larry Bauer, RN, MA (02:14:01):

Celeste, we've shifted gears into talking about what type of activities your child cannot do as well because of having CTD. What are some of the biggest impacts on your child's life? Would you like to share with us?

Celeste (02:14:22):

Sure. I'm located in Charlotte, North Carolina. I have a 10, almost 11-year-old with CTD. So, for us, the biggest impact that we see for him is his ability to self-regulate his emotions, his impulsivity, his tantruming. That tends to be the biggest obstacle between him and just anything on a daily life basis that impacts his ability to interact appropriately with his siblings or peers, impacts him at school, getting on and off the bus at mealtime. It's almost in your constant struggle for us and for Levi.

Larry Bauer, RN, MA (02:15:11):

And is this a daily event?

Celeste (02:15:16):

Oh, yeah, and multiple times a day. It really just depends on what's going on. There are lots of different factors. Some of which, we don't know or can't control internally, but if he wants something that he can't have or if he has to wait for something or if he just doesn't want to do it, he'll just plop right down, whether it's in the middle of the driveway or a road, or he'll just start screaming and engaging in self-injurious behaviors if we're in the house and at mealtime. Then that, in turn, impacts his ability, like I said, to interact with other family members. Sometimes, we can get him distracted and calm down really quickly. Other times, it's a 30-, 45-minute tantrum where he just gets so upset that he doesn't know why he's upset anymore. So then he hasn't eaten dinner and he is more tired, and it just all builds on itself.

Larry Bauer, RN, MA (02:16:18):

Wow. So I'm sure Trey was just mentioning a minute ago about the impact on social relationships that it's almost impossible to have them. Is this similar for your son?

Regina Bogar (02:16:32):

Yeah. Levi has a desperate want to interact with others, and we see this in talking with his teachers at school. He will hug almost anybody in the hallway, or he loves to hug his classmates. However, he doesn't know his own strength. And then, he also doesn't know when to let go, and he doesn't know how or where on the body to hug. So a lot of times, he'll put people in choke holds, or he'll pull them down to the floor. He does the same with his siblings at home. He'll lay on top of them, or he'll hug tightly.

(02:17:08):

He has a nine-year-old sister, a 21-month-old brother, and then a seven-week-old brother. And so we find ourselves constantly having to... We don't want to necessarily fuss or jump or cause attention to what he's trying to do. Most of the time, it's not malicious. He's desperately wanting to interact or play or help or do whatnot. He just has no idea how to, but then sometimes, as parents, we often jump the gun, and we're like, "No, no." That, in turn, then upset him. So then it goes haywire from there. So we try to catch ourselves and just try to be really purposeful. "Oh, that was a nice touch." Even at the park, he wants to play with or wants to interact with other kiddos, whether smaller than him or his age or a little bit older. He'll just sometimes stand there and watch. He'll go up and he'll hit. He just doesn't understand, doesn't know how to do that.

Larry Bauer, RN, MA (02:18:16):

And can you tell us, does he have good days? You said this happens every single day, but does he have good days where the behaviors are better?

Celeste (02:18:31):

Yeah, yeah. I like to say that his behaviors ebb and flow. We'll have a rough season. We just got out of having a rough season where I think pre-puberty is starting to hit. We had a new family member join the family. A lot of it was medication related. We got all of that regulated once we were able to get there. And now, we're in a fairly good season. The struggles are there all day, every day. It's just a matter of if he's able to come out of the tantrum quicker, if he's able to respond to the light touches, or if we're not having to be so close to him in proximity, then ride on top of him.

(02:19:19):

The other day, he handed me the bottle for the baby and was trying to put it in his mouth. And so I was right there obviously with the baby, so I was able to help temper, the push from his hand. So he is not smashing the baby's face, but he'll do nice touches with his sister on good days and she'll respond appropriately, but we have to stay on top of things and anticipate. It really just ebbs and flows depending on the day, depending on everything that's going on.

Larry Bauer, RN, MA (02:19:56):

Okay. Well, thank you, Celeste. Heidi, I was wondering, do we have any comments coming in, written comments coming in on this topic of life impacts, activities that are impacted because of CTDs?

Heidi Wallis (02:20:08):

We do. I think we have three really powerful comments here. Ted in California comments about his son's CTD, "My child's future is limited with a non-independent existence, reliant on other people, agencies and communities for the rest of his life as he is non-verbal and has mental, behavioral, gross and fine motor dexterity deficits." And then, we also have a comment from Susie in Tennessee, "My 21-year-old daughter has GAMT. The symptom that has the most impact on my daughter, family, and people in her life is her erratic behaviors with the possibility of violence on a daily basis. On a good day, I hope to be able to sleep through the night without her terrorizing us."

(02:21:06):

And then lastly, Jenny in Connecticut comments, "My twin boys, who have GAMT, are 12, and I am still tying their shoes, brushing their teeth, helping them to figure out how to move their arms in the shower to wash on their own. I'm still helping them with toileting needs. They want to be independent and be like their peers at school. And it's a struggle as a parent to watch them get left behind in academic sports and other pre-teen experiences. The friendships they should be having right now are non-existent."

Larry Bauer, RN, MA (02:21:45):

Okay. Well, thank you. Yeah. Well, so once again, we're hearing about these basic activities of daily life that are impacted. As well as when we think of typical childhood development, these kids, especially as they get to be teenagers, social lives are such an important part for most teenagers. It sounds like these kids are really struggling. I'd like to ask, does anyone else on the panel, on our Zoom panel, anything else you would like to say about life impacts that... Please raise your hand if you'd like anything else about... Okay, Trey. Yeah.

Trey Wallis (02:22:23):

Yeah, I think some things we haven't necessarily touched on, particularly in my situation where I have one child that's pretty dramatically affected and another child that just takes supplements, there's dietary restrictions as well. And in particular, one thing that comes to my mind is, right now, we're limiting the amount of protein these kids can eat. And that also has an impact. So if you take Louie, for example, he's 11. Like I said, he was diagnosed at birth, so he doesn't have any of the mental challenges that Samantha has, but he's in hockey and he's a growing boy. He's hitting puberty, and he's going to need protein to build muscle and all of those other things. And that's an impact right now. I mean, that's an effect. He's not a big kid, and we're concerned about that. I think while there are some significant dramatic challenges, there's also some other ones that are maybe less obvious, but also challenges when you're dealing with kids with these deficiencies.

Larry Bauer, RN, MA (02:23:27):

Remind us, how old is Louie again?

Trey Wallis (02:23:29):

Louie's 11.

Larry Bauer, RN, MA (02:23:31):

11. How do you keep an 11-year-old from restricting their diet?

Trey Wallis (02:23:38):

It's rough. It's rough. Yeah, there's a significant amount of defense going on in the kitchen from my end.

Larry Bauer, RN, MA (02:23:47):

Wow. Okay. Great. Anyone else on the Zoom panel? Go ahead, Celine.

Celine Wheaton (02:24:00):

Yeah, hearing all the comments and the panelists' experiences, they all resonate with me with regard to feeding and that sort of thing. With Matthew, his creatine isn't getting there. He can eat as much as my husband does, like two things of steak and vegetables, and the whole big serving a rice. And he's still so skinny and below-the-weight chart and hardly ever gets on it. When he takes off his shirt, which is often, he just looks so... We don't feed him enough.

(02:24:52):

CTD affects so many systems, and likewise GAMT, too, but it affects so many systems within your body. You feel like you get ahold of one thing like, "Oh, he's finally feeding better as a baby, and now he's starting to gain a little weight, and then something else comes up." We thought he didn't have seizures for the longest time. And then he started having seizures about three years ago. So it just keeps hitting you with one thing or another. It just gets to be an overload. And then, my biggest concern is even though I'm a careful caretaker as a parent, I love my son, I worry about the future. Who knows who the caretaker is going to be? And if he's having behaviors, are they going to look and see, is it GI causing those behaviors? Is it something going on with his seizure medications, or will they just stuff with a bunch of medication that'll just make him a zombie? I don't know. That's my biggest fear, is about the future.

Larry Bauer, RN, MA (02:26:06):

Okay. Well, thank you very much for sharing that. So for the morning session, we have one more polling question that we would like to go to. Just as a reminder, use your cellphone or a laptop and go to pollev.com/ccds. Once again, it's pollev.com/ccds. And once you go to that site, the question, this last question, our fourth question of the day will come up.

(02:26:47):

One second here. There we go. So this question is, what worries you the most about the person with CCDS' condition in the future? And for this question, you can select the top three things. So we're talking about worries for the future. A is that symptoms will get worse. B is impact on job or school. C is impact on social relationships. D is being able to live independently. E is safety issues. F is being cared for after caregivers pass. G is not being able to communicate their needs. H is developing medication intolerance or side effects. I is impacts on the caregiver's physical and mental health, and J is other. So please enter your top three choices for worries for the future.

(02:27:49):

Right now, the leading choice people are selecting is being cared for after caregivers pass, which we heard several people speak about their concerns about that. Also being able to live independently, which is another aspect of that situation. Worrying about symptoms getting worse. This disease is becoming progressive. Not being able to communicate is also one of the main choices that people are picking. Every single choice has been selected, impacts on the caregivers' physical and mental health, safety

issues, which we heard many times, impacts on social relationships, and impacts on job and school. And we have a few people that have chosen other. But pretty consistently this worry for the future, the main one being selected as being cared for as parents get older, and the caregivers are no longer able to take care of the child. And like I said, being able to live independently is the kind of companion fear with that one.

(02:29:13):

Now, let's go back to our panelists that have been so kind to hang in there with us all morning long. Could I ask Rachel, as you saw that question, what were some of your main worries for the future for your child?

Rachel Cafferty (02:29:30):

I think just who's going to care for him when my husband and I are unable to. We hope that our daughter will take an active role in that, but that's a lot of pressure to put on her as she gets older as well. And just being able to communicate needs and live independently as well. At this point without a treatment or a cure, he won't be able to live on his own and what that will look like for him. And then, will he be able to communicate his needs once he gets older, and will people be able to understand that and look into things a little bit further from him?

Larry Bauer, RN, MA (02:30:00):

And Rachel, remind us how old is your son?

Rachel Cafferty (02:30:03):

Gilbert is 10. Sorry, he'll be 11 in a couple of days.

Larry Bauer, RN, MA (02:30:06):

Okay. And do you imagine, are there... I don't know. I'm sure you're connected with other families. Are there residential places where sometimes kids as they get older can live, like assisted living or...?

Rachel Cafferty (02:30:22):

There are, but they're not very well... It's hard to find staffing for that. And then, there's been a lot of just complaints about the care that is being given at those residential homes and treatment places.

Larry Bauer, RN, MA (02:30:36):

Okay, thanks. Carole, your daughter's a little bit older. I think she's one of the older children that we've heard about today. Can you tell us about your worries for your daughter's future?

Carole Chehowah (02:30:49):

Yeah, aging is the real concern, I mean, aging for her, but aging for us, too. On our side, when you see that, epilepsy has been deteriorating the age. We don't have many information of how CTD evolves when you get older. And so maybe, there will be more symptoms or unknown symptoms or over things evolving the wrong way. So that's one of the key concern. And also, who will take care of her when we're too old or just gone? And as Rachel said about the institution that exists, in France, there's a few place, and we have done to move when Elisa turned 24. So she spend a week in a place and she comes back

during the weekend and the holidays. It's not easy, but she's safer there because there nothing can happen. She cannot be in the middle of the street screaming or yelling or trained to hurt herself. So she's in a very quiet place where people are very skills to take care of these people. So at least we find a place, but it doesn't solve the problem about the CTD syndrome's evolving, and who will look after her when we're gone? She has a little sister, but it's hard to put everything on another kid. She's very involved. She's only 16. But still, if we can have everything put together, that she's better. So our only hope now is the treatment or anything that can improve her condition and make her more relaxed and less anxious for the future.

Larry Bauer, RN, MA (02:33:02):

I was wondering, too, Carole, because of Elise's symptoms, I think you mentioned she has seizure activity, maybe some impulsivity, communication issues, how difficult was it to find a residential program that would accept all of those?

Carole Chehowah (02:33:19):

Actually, we have been lucky, if I can say so, it's because she has the autistic diagnosis, too. And I don't know for the US, but in France, autistic is a big theme for the government, for the research, for everything. So as she has this diagnosis, too, there's special place growing, not much, but a few of them with a lot of money and a lot of skills, people. And we have been lucky because of that. And so it was hard to find, but it's there. It's a wonderful place, although it's not perfect, but nobody hurt her. Then you have to have your list, what's important? To read, to write, to do sports, to do things? Yes, but the most important is to make sure nobody hurt her, nobody rape her, that there's no bad treatment or anything like that. It's sad to say that we have just to have a lower expectation on some things that we think are important because there's things that even more important where we are far away from them.

Larry Bauer, RN, MA (02:34:43):

Yeah. Okay. Thank you so much. Beth, would you like to weigh in on this about worries for the future for your two children?

Beth Robinson (02:34:55):

Sure. In fact, I'm having two such different paths. I had two concerns for Celia who has made a pretty miraculous recovery. My concern for her is the social impacts of the treatment and the disorder, because one day, she will be an adult and she will be a professional and maybe a mother someday. And she still has to administer all this medication. And for Benny, I think similar with other families, it was who will take care of Benny when we're gone? We are at the beginning of that process. He's 18, soon to be 19, and we got guardianship of him. And this is when the hard work begins, thinking about the future, making a will. And like Carole was saying, safety is a huge concern. These are some of the most vulnerable kids, nonverbal, and no safety awareness. So that's always something we think about.

Larry Bauer, RN, MA (02:36:11):

Once again, your two children, it sounds like, from being treated at different ages, you've got different concerns for each one, huh?

Beth Robinson (02:36:21):

Yeah, tremendously different. Their lives have taken two different paths. It's bittersweet, for sure. I know there are other families who are in this situation. Benny will be with us for the rest of his life, and that's fine. He's a really funny, loving kid, who likes to give big hugs and doesn't know his own strength. He's over six feet tall.

Larry Bauer, RN, MA (02:36:46):

Yeah, wow.

Beth Robinson (02:36:47):

We love spending time with him, but we are sad for the opportunities that he missed out on that Celia does have. She will live a very typical life, and we're so thankful for that early diagnosis for her.

Larry Bauer, RN, MA (02:36:59):

Okay, thanks. Heidi, have we received any written comments about worries for the future?

Heidi Wallis (02:37:06):

Yeah, we have some good comments here. Jacob in Florida comments that, "For my son with GAMT, my main focus is making up for lost time. He only started his creating supplements at age five. Had he started years before, the impact of his condition would not have been as severe." Related to Carole's comment, I have a comment from Dan in California that he is worried that the rarity and lack of knowledge from medical providers is impacting his son with CTD and his therapies that are made available to him. I also have a comment from Jolene in California. She comments about her son with CTD, "The amount of care my son requires has caused us to drop from a two-income family to a one-income family. And my biggest fear is that what will become of my son with extremely limited communication skills and severely limited cognition once I am gone?"

Larry Bauer, RN, MA (02:38:21):

Okay, thanks. Yeah, that one comment was similar to what Carole said, that sometimes having an autistic diagnosis along... I can imagine that with CTDs being so rare that many, many people, many systems probably have never met a child with this condition. And that sometimes maybe having an alternative diagnosis actually could be helpful to get, have the help you need. Let's see, who did we not... Celine, would you like to weigh in on this about your worries for the future?

Celine Wheaton (02:39:00):

Yeah, I mean, I touched on it earlier, just worried about all the things that CTD affects and how Matthew will be relying on other people to take care of him once my husband and I are gone. He doesn't have any siblings, and we're a little bit older. Yeah, we try to stay as healthy as we can to keep up with Matthew and to live as long as we can and be sane. I don't know. It is physically draining taking care of a child that's impacted by GAMT or CTD. And the older they get, they're getting stronger, we're getting weaker. So that's a big impact.

PART 5 OF 10 ENDS [02:40:04]

Celine Wheaton (02:40:02):

So that's a big impact. Yeah, I'm very frightened about the future. It's something that I think about. Try not to think about every day, but it's always in the back of my mind.

Larry Bauer, RN, MA (02:40:11):

Yeah. Okay. Thank you so much. I see we have a caller on the line. We have Laura from Washington with a child with CTD. Laura, are you with us?

Laura (02:40:26):

I am. Hi Larry. Thanks. I have another angle on the family burden. So some of us definitely, for some of us is our inherent conditions. In fact, for me, I'm a mosaic for CTD, and that has implications for inspirations related to fertility. So I have a eight-year-old with CTD and we have tried for a long period of time to consider getting him a sibling so that we can anticipate potential needs further down the line. Same thing, not easy to have siblings care for a disabled person, but at the same time, it's probably the best option. And the fact that these are inherited conditions and the fact that we don't know, for example, the full implications for females limits a lot of options for families, not to mention the financial cost and the overall burden of dealing with IVS and other reproductive screening methods.

Larry Bauer, RN, MA (02:41:21):

Okay. Thank you. And do you have any other concerns for the future as you think ahead?

Laura (02:41:30):

I think, in general, my analogy for this is that for Rohan, for my son, there's a very narrow window of equilibrium where he can focus or he can, so the stars have to align so he can acquire any skill and requires a tremendous amount of effort. My concern there is that that window, and when I became a parent, I imagine my kid becoming more and more resilient and learning more things. And basically that narrow bandwidth increasing over time. This is how you see your kids becoming independent. One of my fears for my son and in general children with CTD is that the opposite is happening. That bandwidth where things are optimal, where the children can communicate, it's actually getting narrower and narrower, where they can moderate their emotions, they can pay attention to stimuli.

Larry Bauer, RN, MA (02:42:22):

Okay. So sounds like, yeah, progression of symptoms is something of great importance to you. So yeah, thank you for sharing that. Heidi, is there anything else that comes to mind on the topic of symptoms, life impacts, fear for the future? You're a mom with two kids.

Heidi Wallis (02:42:43):

I think Trey is raising his hand. I'm overwhelmed with the input from everyone. And I think the commonalities between GAMP and CTD and this last topic just, I think, hits us all really hard when we think, how does my child do this without me? So, I don't have much to add.

Larry Bauer, RN, MA (02:43:07):

Okay, thanks. Trey, did you have a final comment?

Trey Wallis (02:43:11):

Yeah, I just wanted to make a comment when it comes to treatment, because I think that's what this is all about. I think there's kind of two phases that you can see with parents and those affected by kids with creatine deficiencies. When the children are young, the goal for parents is really how much progress can I make on this? How quickly can I get this taken care of so all of the development markers for kids can be met? And in my experience, as kids get older, you know that that's a shrinking window. You know that that capability starts to diminish as they age. And then, I think what's interesting in this conversation about where do we go in the future, you notice that sort of shifts to caregiving and long- term things. And that's also similar to the attitude that parents develop, right? At a certain point, there is acceptance.

(02:44:08):

When they're very young, you don't want to accept it, right? You want to push and you want to drive and you want to try to get something, you want to try and get the best for your child. But over time, after that diagnosis, you have to accept it. You have to love that child. You have to be okay with as far as they can get. What's important about this future discussion is seeing incremental progress in treatment. That is the number one benefit when we think about long-term care. We can talk about living independently, we can talk about all that other stuff. But I think if each one of us could see treatments that are providing incremental progress for these kids, that's the biggest relief we would find, by far.

Larry Bauer, RN, MA (02:44:51):

Well, thank you so much for sharing that, Trey. People are going to think you're a plant, but it's not. Actually, Trey's comment is the perfect segue into our afternoon session. We're going to spend the entire afternoon talking about treatments from various different perspectives. So for now, I'd like to thank our panelists so much. Thank you for everyone who called in, that wrote in, and everyone that's been in attendance. We'll now take a lunch break and will rejoin at the same link that you joined the meeting. We'll be back at one. Thank you.

PART 6 OF 10 ENDS [03:12:04]

Larry Bauer, RN, MA (03:15:18):

Welcome back everyone to the externally led patient focused drug development meeting on cerebral creatine deficiency disorders. This afternoon we'll be shifting gears a bit. The morning session, we focused on CCDS symptoms and life impacts and the discussion. This afternoon, we're going to change a little bit and focus more on treatments for CCDS as well as hopes for the future. My co moderator, Heidi, will introduce our next speaker. Heidi.

Heidi Wallis (03:15:46):

Thank you, Larry. This afternoon, CCDS expert is Dr. Nicola Longo, who will be discussing CCDS treatments. Dr. Longo is Professor of Pediatrics and Pathology at the University of Utah, Chief of the Division of Medical Genetics, Director of the Metabolic Service in the Department of Pediatrics, Medical co-director of the Biochemical Genetics and Newborn Screening Laboratories at ARUP Laboratories in Salt Lake City. Dr. Longo follows many patients with CCDS and has an active clinical research program directed toward the development of new therapies for metabolic disorders, including CCDS. He also has an active interest in advancing newborn screening. Recently, Dr. Longo, along with the Association for Creatine Deficiencies nominated GAMT deficiency for inclusion on the federal Recommended Uniform Newborn Screening Panel or RUSP. We are excited to share that GAMT was officially approved for the RUSP earlier this month by Secretary of Health and Human Services, Dr. Becerra. Identifying GAMT in the

newborn period is going to be a game changer for future generations. Thank you, Dr. Longo, for your work towards this major accomplishment. And now over to you, Dr. Longo.

Nicola Longo, MD, PhD (03:17:17):

Thank you very much for the nice introduction. Today I want to talk briefly about the existing therapies for cerebral creatine deficiency syndrome, focusing on what we know and what we do not know. These are my disclosure. And as you have seen from the introduction, there are three different creatine deficiency syndrome caused by deficiency in the synthesis of creatine. The first one being AGAT deficiency, the second one being GAMT deficiency, and the third one is caused by defective creatine transport inside the brain. The different condition have different therapy. Let's start from the first one, which is AGAT deficiency.

(03:18:12):

This is the rarest of all of the creatine deficiencies syndrome and it is lightly different from the others in that there are prominent muscle symptom. In this condition, creatine cannot be synthesized because the first enzyme here is missing and all of the problem are caused by the lack of creatine inside the brain. And in fact, the therapy is giving creatine at high dose divided into three to six divided doses. What we know is that if therapy is started very early because of family history and potentially one day because of newborn screening, symptom are prevented in individuals with this condition. So among the three different condition causing creatine deficiency syndrome, AGAT deficiency seem to be the easiest to trade with a single medication, which is creatine.

(03:19:24):

When we move to GAMT deficiency, which is the second disorder of creatine synthesis, there are more problems. Why? Because not only there is the lack of creatine in the brain, but also the accumulation of guanidinoacetate, which is an intermediate in creatine synthesis which cause neurotoxic effect. The therapy is much more complex. If we go back to the slide showing the reaction, what we need to do we need to decrease the synthesis of guanidinoacetate in addition to providing creatine the end product of the reaction. The way to decrease guanidinoacetate is decreasing the amount of arginine by a protein limited diet and also providing ornithine. Ornithine, it is one of the products of the reaction, and by feedback inhibition, giving an excess of ornithine can decrease the synthesis of guanidinoacetate. Finally, we can try reducing glycine by providing sodium benzoate that will bind to glycine generating puric acid, which is created in urine.

(03:20:57):

So the therapy here again involve all of this medication creatine monohydrate like we did in AGAT, ornithine at high dose and then dietary restriction of arginine in that there is needs to be a diet limiting the amount of protein and plus the supplementation of sodium benzoate that can reduce glycine level. Now, why do we do this type of therapy? The reason that we know that there is a direct correlation between arginine and guanidinoacetate. There is even a strict correlation between glycine level and guanidinoacetate. And at the same time, what we know that by giving sodium benzoate we can reduce glycine level and decrease also the concentration of guanidinoacetate. That it is why we do all of this therapy. What is the effect of this therapy? The effect of these therapies that if we give them early on because of family history or because of newborn screening, children appear completely normal.

(03:22:10):

Now we don't have a lot of experience with them, but all people, all individuals treated early on have shown so far normal development up to about 10 years of age. So the therapy seems effective if started

early on. There are still some gap. Why? Because even with the best therapy, we can never normalize guanidinoacetate in plasma of patient with GAMT deficiency, the most difficult condition to treat of all three is the disorder of creatine transport. This condition present like non syndromic intellectual disability is very difficult to diagnose and it is one of the X-linked form of intellectual disability. This condition is different from the others because level of creatine and guanidinoacetate are normal in plasma and the secretion of creatine is only increased in urine.

(03:23:20):

The problem here is that the fact that creatine cannot enter inside the brain. In addition, the same transporter that transport creatine transport the precursor of creatine, guanidinoacetate. For this reason, one cannot supply the immediate precursor of creatine to this patient. Now, when one look at the efficiency of therapy, the therapy is done by providing obviously high dose creatine, arginine and glycine that are the precursor of creatine, and obviously they would allow the synthesis of creatine within the brain. And some patients actually respond to this therapy with a qualitative improvement of clinical manifestation. It is a qualitative improvement because we don't have any control study. And in general, patient who respond the best are people who retain some residual creatine transporter activity. So in other words, people in whom the mutation does not completely wipe out the function of the protein.

(03:24:43):

Some additional therapy have been attempted and this consists in the administration of S-adenosyl methionine, which is the donor of the methyl group in the synthesis of creatine. S-adenosyl methionine is the donor of the methyl group to guanidinoacetate and my favored formation of creatine within neuronal cell. The second therapy that has been described only recently and only in two patients with adults with creatine transport deficiency is the administration of betaine. Betaine is also a methyl donor and could do the same job of S-adenosyl methionine, but at the same time could have also other different type of mechanism of action. And this seems to be effective in improving behavior in some patient with creatine transport deficiency. Now, what is on the horizon? So for cerebral creatine transporter deficiency, there are no active interventional clinical trial. Hopefully we will have some clinical trial with additional therapy that are in animal study.

(03:26:06):

This include administration of intranasal creatine that could reach the brain directly to vesicle transmitted by the olfactory nerve. There are also creating analog that have been tested in the past and some of which might come back and provide an alternative route for creatine to enter in the brain. And finally, gene therapy for GAMT deficiency has been described animal model and seems very effective. We still don't have a gene therapy for creatine transporter deficiency. Results are mixed based on the fact that patient completely missing and mice completely missing the gene for the capacity to make the creatine transporter might have a reaction to the creatine transporter once expressed on the plasma membrane. So in summary, we have seen that there are existing therapies for some of the creatine deficiency syndrome. Some of them completely lack an effective therapy and animal models are providing answer for only some of them. Thank you very much for your attention. I want to pass the microphone back to the moderator.

Larry Bauer, RN, MA (03:27:26):

Thank you so much, Dr. Longo, for that great presentation. To help us get started this afternoon, I would like to review some of the topics and questions that we will be focusing on today. So for session two,

which will be focused on perspectives on current and future approaches to treatment, the first topic is what are you currently doing to manage you or your loved one's CCDS symptoms? Number two is how well do these symptoms treat the most significant symptoms and health effects of CCDS? Number three is what are the most significant downsides to you or your loved one's current treatments and how do they affect daily life? And finally, short of a complete cure, which we know everybody would like to see, what specific things would you look for in an ideal treatment for CCDS and what factors would be important in deciding whether to use a new treatment? So to help us get started on these topics, we will be hearing from a group of panelists that have prepared statements in advance of the meeting. So I'd like to welcome Susie, Leif, Christina L., Christina W., Kayla, and Nathan.

Susie Richards (03:28:44):

Hello, my name is Susie Richards. I'm the mother of Daisy. She is 21 years old and has GAMT deficiency agency. Reflecting back on the past 21 years of Daisy's life with this disease brings so much sadness. My life has consistent of moment to moment problem-solving to keep everyone and everything safe from Daisy's ever fluctuating behaviors. Extreme behavior problems have been the constant symptom of this horrible disease and have affected every aspect of Daisy's in our lives. GAMT has left Daisy severely intellectually delayed with severely limited communication. Daisy was one of the first GAMT cases diagnosed in the US when she was two years old. I was told she would need to take supplements to regulate this metabolic disease the rest of her life. Being a very young mother at the time and not knowing the extent of damage that not properly giving her these supplements, I could damage her brain so severely.

(03:29:56):

Daisy started having seizures around two years old. They were drop seizures. She would have up to 50 or more a day. Many trips to the emergency room were involved. The fear and uncertainty of living with this daily was chaos. These seizures were never fully controlled and they continued until she was nearly 14. This was just one of the many obstacles resolving from GAMT. Another daily obstacle was giving Daisy the daily supplements. Since I tried and failed at giving her the powders by way of food or liquid, I decided to compound over 60 pills a day knowing she could swallow pills. This turned into a monumental task, encapsulating the pills, trying to have Daisy swallow this large amount, this continuum for years with a lot of times not being able to give her the prescribed dosage, resulting in what I think the damage caused to her brain.

(03:30:58):

Sleep is another huge obstacle for Daisy. She will wake hours of the night. Because of her severe intellectual incapacity, she does not understand the concept of time, which you can imagine all sorts of complex obstacles this brings to life. Upon waking in the middle of the night, she'll storm into my room crying or hitting and pulling me. Many times I had to call the police because of the extreme violence of some of these episodes. I now live in a constant state of fight or flight from the unpredictable waking episodes. As I stated, there have been encounters with the police to help me get the behaviors under control. At one point it took five officers to restrain her eloping, hitting, biting, destroying properties come up many times in our lives. This particular time ended in admitting her in the hospital and putting her in restraints and secluded from everyone. After that night, my heart was permanently broken. I have an older son and two younger than Daisy. GAMT has had an enormous effect on their lives. My older son did not have much of a childhood because of all my attention, focused on Daisy's care. He left home as soon as he could at 18, as not to be around the behaviors any longer. My younger two sons have had to endure a lot also. She becomes violent with them and I'm constantly in protection mode. My house is

full of broken doors, windows, deadbolts. I lock from the inside. We do not go on trips. I cannot attend most of my son's baseball games or musical events. Virtually no public events in fear of meltdowns. The biggest turning point in our lives from enduring the constant struggles of this disease was in 2018 when I had a mental breakdown.

(03:32:56):

I had to be hospitalized. My children left in the care of my oldest son, including Daisy. He had no idea how to take care of her. The state was going to step in. I was going to possibly lose my kids. During this time, I realized I might need to give Daisy up. It was heart-wrenching. Nobody could care or love her like me. It felt as if I was giving up my two-year-old. Fast forward to today, Daisy is still living with me and my two kids.

(03:33:29):

It is still ongoing chaos in our world. She was just suspended from school for hitting another. I live in constant fear of her hurting someone. I will be taking care of Daisy the rest of her life. She is my life. This disease is taken so much from her. I have so much guilt and shame that maybe I could have done something different and her brain would not have been damaged to this extent. If there is a sliver of hope that there maybe help with a drug that may prevent this monster of a disease damaging another life and family, I see her every day in this dysfunctional body wanting to express herself, wanting to communicate like us. I ask you, please remember Daisy. Thank you for listening to our story.

Leif Law (03:34:27):

Hi, my name is Leif Law. My wife is Mikaela Law. We just this week of Christmas relocated to Star, Idaho. We are the proud, blessed parents of three children, Max, Mason, and Sadie. Max is our oldest child. Max was born in 2009. Max just turned 13. About six months after birth, we started to notice that Max was not hitting his developmental milestones. With the help of our pediatrician, we were able to get Max a MRI. We were very fortunate to have an experienced doctor who requested and recognized the specific MRI spectrum that identified GAMT. Max was diagnosed with GAMT at the age of one. We were fortunate at the time to live in Utah and have access to the experienced medical team at the University of Utah. We immediately began a regimen of supplementation three times a day. This supplementation consisted of three things all in powdered form, creatine, ornithine, and sodium benzoate. These supplements needed to be precisely measured out for each of the daily three doses that Max required and packaged individually for use. Over the years, we have had a lot of trial and error with regards to the delivery mechanism for these powdered supplements. They're not palatable, very, very harsh tasting. When Max was quite young, we would mix them in a large syringe with water and give it to him by mouth. This was rough and often a struggle as he was not willing to swallow it easily. As he got slightly older, we began to experiment with mixing the supplements with other soft foods. Applesauce worked for a period of time, but then that quickly wore off and lost its luster. As Max has gotten older and grown, the amount of supplement increases, this presents an ever increasing challenge and problem to address. We currently mix the supplements with yogurt.

(03:36:31):

Due to the harsh taste and increasing amount, each of the daily doses takes Max a minimum of 30 minutes to consume. Max's day and ours to a large extent always revolves around getting each of his three doses in and doing it at the correct time or within the appropriate time window. For Max to be able to consume the supplement mix, it has to follow food or a meal. Otherwise, it is too harsh on his stomach and he will vomit. The harshness even after this many years, frequently makes Max gag even

when he takes it following a meal. If we try to push him to take larger bites or to eat faster due to any time constraint, he gags or throws up. Basically it takes as long as it takes every time. Max also has to be supervised to ensure he takes all of the mixture. We recently went through a period within the past year where we did not supervise him as closely and trusted that he would do it on his own.

(03:37:31):

We began to notice small changes and deficits in his mental acuity, his speech, and his energy levels. Then one day we happened to catch him throwing out part of his supplement mixture. He had been hiding that from us and disposing as much as he could just because he hated taking it so badly. This was probably one of the lowest points that we have had with Max in years. It was a reminder that we don't know how self-sufficient Max will become as he gets older. He doesn't cognitively understand what is going on inside him and his tested IQ is very low and it's difficult for him to grasp concepts. Max has an IEP at school and he goes to regular classes. He is operating at the low end of normal scholastically. Max is very involved in sports and competes at his grade level. He excels at basketball and that is where he puts a large portion of his focus.

(03:38:26):

He has been able to overcome some of the physical challenges brought on by his GAMT with practice. As Max now enters his teenage years, there are a lot of challenges and ongoing questions. How will GAMT affect him going through puberty? Will he grow at the same rate? Will GAMT affect his thought process and his negatively as he goes through hormonal changes? How will his confidence be affected? This one is big because he is realizing more and more that he has challenges that other kids just don't have.

(03:38:59):

Will GAMT affects his emotional state? Will he be able to continue to work towards self-sufficiency or will he digress? Can he gain more confidence? The supplement mix that Max has been taking has not changed since his diagnosis 13 years ago. An ideal treatment would be easier to take and less time consuming. The amount of powdered supplement required is only getting bigger. There is the option of taking capsules, but the number of capsules needed for each dose is very prohibitive. Also, the current prognosis is that the best we can hope for is the status quo. The supplements work to keep levels close to where they should be. So far, there is nothing emerging that would have the help of reversing some of the damage or improving cognitive ability.

Christina Lin (03:39:50):

I remember when I was seven years old, visiting the Statue of Liberty in New York City and standing in line to go through security in order to climb the steps to the top of this amazing structure. I was filled with excitement until my family was pulled aside by security guards so they could examine the vials of white powder that my parents were carrying. As my mom tried to explain to the guards what the white powder was for, I hid behind my dad's legs, scared that we would get in trouble, and embarrassed that everyone in line was staring at us. My name is Christina and those vials of white powder belonged to me. I was diagnosed with arginine, glycine, amidino transferase deficiency or AGAT deficiency when I was 16 months old, and I've been treated with creatine monohydrate powder since then. My parents tell me that prior to treatment, I had gross motor delay and wasn't gaining weight. But once I started creatine treatment, my motor skills quickly improved and I started crawling and then started walking in just two short months.

(03:40:51):

My body also started to function better and I started to gain weight again. In addition to taking creatine supplements. My treatment also initially included physical, occupational, and speech therapies. It became quite obvious that early diagnosis and treatment of AGAT deficiency was so incredibly important, and I am now a college student studying public health and psychology at UC Berkeley. Even though I had early diagnosis and treatment, I realized that the rarity of my condition came with many challenges. It was hard to feel normal when my kitchen counter looked like a lab bench with multiple vials, powdered filled containers and a digital medicine scale. It was hard to feel normal when classmates stared at me when I poured a mysterious substance into my drink at lunch or when I had to sneak out a day-long Nutcracker rehearsals in order to gulp down my medication, so the other dancers would not notice.

(03:41:47):

Growing up, all I wanted to do was fit in, so I tried everything I could to avoid having to explain to others why I needed to take medicine. It has also been unclear how much creatine monohydrate I needed to take. Because of how rare my condition was, no one really knew the proper dose for me. My dose was adjusted multiple times over the years as we were trying to optimize the amount of creatine in my body while also monitoring for side effects to my kidneys with regular kidney ultrasounds and blood and urine tests. I was taking creatine four times a day and my parents had to find creative ways to mix the white powder with something I would like to eat or drink. Each day, my parents would measure out the creatine powder and store them in vials so that we could take them out with us or I could take them to school.

(03:42:34):

When I was a baby, my parents mixed the creatine powder with milk or juice and gave it to me in a syringe. As I got older, my parents mixed my medication with ice cream, which is great, but just not practical, I guess not the healthiest either. I also convinced my doctor to let me reduce the dosing frequency from four times a day to three times a day since I hated to be constantly interrupted with what I was doing in order to take my medication. I now measure out my own medication and mix it in whatever I like, whether it be in my smoothie or a favorite boba drink. But nobody liked taking medications, especially children. Wouldn't it be great if creatine actually tasted good? If I could change my medication, I would not only make it taste better, but I would also like it to be more convenient to take and would like to see a chewable tablet or pill that can have the same effect as the powder.

(03:43:26):

It would be even better if the medication can work longer in the body so that it can be taken just once a day instead of three or four times a day. I'm definitely willing to participate in research studies that may help further understand my disorder and treatment and have already contributed blood samples for research. I hope for clinical trials in the future that would look at proper creatine dosing and side effects, as well as discover different methods to deliver creatine. If I were to participate in a clinical trial, safety and lack of adverse side effects would be important to me. I still worry about how AGAT will affect me in the future. For now-

(03:44:03):

I still worry about how AGAT will affect me in the future. For now, it seems that the side effects from creatine are minimal for me and can be monitored. But what if this changes? How do I know there won't be any long-term side effects to taking creatine for the rest of my life, especially at the high dose that I am on? Could gene therapy even be a possible treatment arc here? I still have my whole life ahead of me and I hope that someday I can even stop taking creatine as a possibility. Even though there's so much

uncertainty with living with a rare disease, I'm thankful that I am healthy and can share my story with all of you today.

PART 7 OF 10 ENDS [03:44:04]

Scarlet (03:44:38):

Hi, my name is Scarlet. I am 13 years old living with CTD. These are my parents, Christina and Zigmas, who'll be here to share my story.

Zigmas Woodward (03:44:52):

Our daughter, Scarlet, is fairly well functioning in general and goes to a typical school with assistance offered to her through her IEP. However, Scarlet had a very difficult babyhood and childhood due to the symptoms she faced and continues to face. As a baby, she never slept for more than 90 minutes at a time for the first three years of her life. She had night terrors and wasn't able to self soothe to any degree. She had breath holding spells as a toddler, which caused her diaphragm to freeze and her not to be able to take a breath until she fell unconscious. Then, she developed a seizure disorder at age five. Currently, she struggles with intellectual delays, social isolation, and a general difficulty in maintaining outbursts, as well as sensory issues that make self-care and daily hygiene uncomfortable and difficult to maintain. She will likely not be able to care for herself alone as an adult.

(03:45:42):

To us, the seizure disorder is the most fearsome of her symptoms as seizures can be deadly. Scarlet has had multiple seizures where she stayed in the seizure for up to an hour and had to be hospitalized for days. Currently, we have her on an anti-seizure medication called Trileptal, which controls the seizures for the most part, but there are still breakthrough episodes. She needs regular blood draws at the Children's hospital to check her levels of medication versus body weight and her sodium levels. These blood draws and hospital visits are stressful and painful for her, but she's always a good sport with a promise of a Target shopping trip for a reward. To control the seizures in the past, we were given options for the powder regimen of creatine, glycine, and arginine, which have been effective in other versions of creatine disorders but not hers. It was also extremely difficult to get her to get over the taste and actually get the amount of powder in that she needed.

(03:46:37):

Also, it smelled and tasted like a garbage bin the morning after a fish fry. She was also at one point advised to adhere to a strict diet limiting her food to just plain meat and fat in order to put her body in a state of ketosis. Even a cucumber had too many carb for her to consume in a day. It was basically a diet of butter, cheese, and ground beef. This was obviously untenable, especially for a member of the family with two other siblings who would be eating normally. Other symptoms that we try to address have to deal with behavior, self-regulation, speech, and the ability to focus and understand what she's trying to work on.

(03:47:16):

These issues are addressed by folks at our school who work with her through her IEP where she has behavioral intervention, speech therapy, and a number of special education teachers. She works on these issues inside her class as well as in special meeting rooms when she's pulled out of class. These have been somewhat helpful, but realistically she's just getting through the school day and going

through the motions, but she's not thriving and she's not really learning at her full potential. This is due to many factors, but there are few alternatives available to remedy to this reality.

Christina Woodward (03:47:50):

Other than these current interventions, there are no options for treatments and no cure. We just muddle through, hoping that each family outing can be navigated without a seizure or more commonly without a meltdown that causes each member of the family extreme amounts of stress and anxiety. We have to try to assess each situation in terms of setting her level of distress and possible solutions, which sometimes can help and sometimes can make things worse. No two meltdowns are the same and each outcome is an unfolding surprise in real time for all of us. Scarlet can't help her outbursts and she feels terrible after and wants to come apologize and cuddle. It's exhausting for every member of this family.

(03:48:32):

If we could somehow improve her ability to understand and maintain her nervous system and reactions, it would improve her life and ours exponentially. I'd like to touch on one detail of this disease, which is that females and males are affected somewhat differently. So far, generally, males have only been included in studies as far as I understand it. Males are generally more severely affected by this disease while females can present along a spectrum of severity with CTD. For our family, we feel if there were some way to calibrate any kind of therapy that would allow for Scarlet to come closer to her fullest extent of health, this would still be a highly valuable therapy for us. I wish that females with CTD would be included in all research studies for new treatments.

Kayla Williams (03:49:23):

Hello, my name is Kayla Williams and I am the mom of Crosby. Crosby is four years old and has CTD. We live in a small community in Wisconsin with my husband Sid and our one and a half year old son, Maddox. When Crosby was one month old, he was diagnosed with reflux and laryngomalacia. Because of poor weight gain, we had to supplement with extra formula. Once he hit four months old, we were able to stop the reflex medications. He also started with baby food at this time and weight gain was no longer an issue. The rest of his first year was fairly uneventful. He sat around six months, crawled maybe a little later than normal, and was taking a few steps on his own. Then a couple weeks after his first birthday, he had his first seizure and had to be flown by helicopter one and a half hours away.

(03:50:13):

Crosby had another seizure eight weeks later and then began Keppra twice a day. He made it seizure free for one year and two days before waking up New Year's Day of 2021 with a seizure that we couldn't get him to come out of even after administering his emergency seizure medication. This time, he needed to be taken by ambulance to our nearest hospital a half hour away. At this point, we upped his Keppra dose, but he had another seizure in April, July, and September of that year. Crosby was also not hitting other milestones. Most notably, with his speech. He would have a word or two, mostly approximations, and then they would be gone. Although he would take steps on his own before his first birthday, he wasn't fully walking until he was 17 months old. By the time Crosby was two years old in October of 2020, he started speech therapy and the speech therapist would keep an eye on other areas of development.

(03:51:13):

Eventually, the seizures began again and we still hadn't seen much growth in his speech skills. Crosby was still non-verbal and still struggling with fine motor and gross motor tasks. He eventually had genetic testing and a seizure panel and was also referred to an audiologist. Crosby started with occupational

therapy and had an EEG to see if he was having more seizures that we didn't know about. In July of 2021, we found out that Crosby had CTD, a rare and currently untreatable genetic condition. It was a bit of a blur, but I remember hearing things like intellectual disability, seizures, ADHD, autism, and speech delays. Even though we knew Crosby was behind developmentally and we were happy to finally have answers, it was still not easy news to hear. It is such a helpless feeling to find out that your child has something wrong and there isn't anything that you can do to fix it, change it, or make it better.

(03:52:18):

In September of 2021, we met with our neurologist for Crosby's EEG. He upped his Keppra dose again and thankfully, we are now over a year seizure free. We also started three supplements at that time, creatine, glycine, and arginine. Once Crosby turned three in October of 2021, he started early childhood at school. He attends three mornings a week and is able to receive his speech, occupational, and physical therapy there. Crosby still did not make much growth with his speech, but he did make a lot of gains throughout the school year last year. This past summer, we spent two to three, three days a week going to appointments for speech, physical, and occupational therapy. His fine and gross motor skills saw more growth than his speech, but we are still happy with the difference that therapy made. The neurologist who treats his C T D recommended stopping the arginine and glycine.

(03:53:13):

The arginine tastes really bad and we couldn't get him to drink anything with the supplement, so we are now currently just giving the creatine. This is much easier to get him to drink and we are not sure if we see much of a difference, but as long as we can get him to take it, we are going to continue with it. For our family, a cure or treatment would mean that we wouldn't have to give seizure medications and supplements every day. It would mean that we could travel without making sure we remember to pack his emergency medications. Crosby is such an easygoing kid, but our hope is that a treatment would be more than just seizure management. We hope that a treatment would also help with his speech and intellectual development. I would love to know what he's thinking, how he's feeling, and what I could do to help him.

(03:54:01):

He currently can't tell us what's wrong when he cries or how we can help him when he's sad as he has less than 15 total signs and words. We also hope that a treatment would help him to build independence with skills like dressing himself, using utensils to eat, and even being potty trained, with a long-term goal of him eventually being able to lead an independent life as an adult. The thought of putting my four-year-old through a trial is scary, but so is not trying it. Our biggest determining factor for whether we would participate in a trial is Crosby's health and safety.

Nathan Vandenberg (03:54:40):

Hello, my name is Nathan and I have three wonderful boys, Elijah, Simon, and Ezra with creatine transporter deficiency. In looking at current treatments, it's important to first talk about our most pressing symptoms. My boys' most acute treatable symptoms are seizures and GI issues. With all three boys having epilepsy, Simon who is a currently has the most severe seizures, which can occur multiple times a day and last at least three minutes per episode. To treat his intractable status epilepticus seizures and abnormal neurological activity, Simon takes seven different seizure medications twice a day in doses that range from a modest three milliliters for the Epidiolex all the way up to a massive 22 milliliters for phenobarbital. Simon's brothers also take multiple seizure medications to treat their seizures and abnormal neurological activities. In addition to medication interventions, Simon has also received

surgical treatments in the form of craniotomy and frontal lobe resection to slow down his seizures, which unfortunately did not work.

(03:55:45):

The seizure treatment regimen for all three boys has evolved and as one medication becomes ineffective, it is either replaced or supplemented by another medication. Further, given his high resistance to or complete ineffectiveness of most emergency anti-convulsants, unique protocols have been put into place to respond to any seizures that occur. Simon has seen his medications slowly increase over the past year as he appears to build up a tolerance to his existing regime. The treatments for Elijah and Ezra are treating the seizures very well, but Elijah has gone through periods of severe seizures in which a single episode can last more than 18 hours. Unfortunately, despite his care team's continued commendable efforts, Simon continues to see seizures increase in length and occur with less and less dwell time between individual seizures. There are still many challenges and worries even with Ezra who has the least significant seizures. GI issues are also impactful, primarily in minimal weight gain and deficiencies in certain vitamins and minerals.

(03:56:52):

To treat their GI issues, all three boys have G tubes in placed. Due to strong reflux and delayed stomach emptying, each child must have a special vented feeding setup, which must be individually taped and altered each night to prevent cinching and tangling. Additionally, each child's is on medications to treat reflux, GERD, and appetite boosters. The GI treatment has remained more consistent over time than our seizure treatment, but as with our approach to seizures, each child is consistently monitored and feed rates and medications are adjusted based on illness, weight loss, or other environmental circumstances that lead to decreased caloric intake. Having got his feeding tube later than the other two boys, Elijah initially saw frequent hospitalizations associated in large part with a lack of appropriate weight gain. Treatment for weight loss issues are relatively successful for all three boys and that they have all increased weight enough to remain out of the danger area.

(03:57:48):

The weight increase, though perhaps less significant than we prefer, has offered the boys a buffer to keep them out of the hospital and let us rest just a bit better at night. Given current growth trajectories and medication requirements for the three boys, they'll unlikely be free of their feeding tubes or supplemental feeding anytime soon. Thankfully, for Elijah and Ezra, seizure impact on daily life are primarily involve planning considerations for the possibility that seizures will happen. Current treatment plans do not have significant side effects, nor do they pose significant hardships or discomfort. Simon, on the other hand, has seen nearly every aspect of his life impacted by the treatment of seizures.

(03:58:31):

The massive doses of medication caused Simon to sleep for large portions of the day, sometimes leaving him awake for as little as four to five hours. While awake, Simon is often too dizzy or disoriented to get up and walk around or play, and it's not uncommon for him to have days when he can only be up and active for less than three hours. Further, between tests and surgeries and visits to the doctor, the time Simon is spent in the hospital can be measured in months or in weeks. Downsides and impacts to our daily life involving GI issues are minimal or at least their comfortable routine. Each of the boys requires a special bed, at least in part to prevent feeding tube mishaps. Trips to or outings are always require bolus feeds and extra planning is necessary. For us, ideal treatments for CCDS would simply keep help keep our kids safe and put our minds at ease for preventing life-threatening seizures and risky weight gain, lack of weight gain. While these outcomes seem minimal, it would truly mean the world to a parent who has

watched their child seize for 18 hours straight or be admitted to the hospital for three weeks for an emergency feeding tube placements.

Larry Bauer, RN, MA (03:59:49):

Thank you, Nathan, and thank you to all the panelists that shared their statements that they had worked on preparing. We really appreciate the work and for you taking the time to share your stories. At the moment, we're joined in the studio with Regina, Gina, Dan, Christina, and Beth. Thank you all for joining us live today. Before we ask any of you questions, I'd like to go back and do a polling question to start off the afternoon. So just as a reminder to participate in the polling, this is for patients and caregivers only, but please go to a browser on your cell phone or your computer and open up PollEV.com/CCDS. You'll see this URL at the top of your screen, and the question that we have is what medications or medical treatments has the person with CCDS used either currently or previously to treat CCDS symptoms, and please select all that apply.

(04:00:55):

So A is creatine monohydrate, B, L-ornithine, C, Sodium Benzoate, D, arginine, E, glycine, F, Betaine, G, pain medications such as NSAIDs or prescriptions, H are anti-seizure meds, I are sleep medications, J are anti-nausea medicines or laxatives, K, behavior medicines such as for ADHD or anti-anxiety drugs, L is supplements, multivitamins or other types, and M is that you've not used any medications or medical treatments, and N is other.

(04:01:39):

So as the answers are coming on, we're seeing everyone's responses in real time. As I said, we're seeing the percentages of the responses as people respond. I see that nobody is saying that they've not used any medications or medical treatments. And so far, up on top of the list is creatine monohydrate. Secondly, anti-seizure medications, and then other supplements is also getting a lot of responses. We're also seeing arginine, glycine, L-ornithine, which we've heard are treatments that people frequently use. Nausea, medicines, behavior, medicines also being used, and there's a fair number of people that are using other types of medications. But as they come in, the creatine monohydrate, that has consistently now stayed up on top as the most used treatment for CCDS.

(04:02:55):

Okay. Well, let's go to the next polling question if we could. There's one more I'd like us to consider. So this question, is besides medications and treatments, either current or previous, what has the person with CCDS used to help manage their CCDs symptoms? Select all that apply. So these include things like A, physical therapy, B, occupational therapy, C, speech therapy, D, school adaptations, E, dietary changes like low protein or gluten-free. F is leg braces or orthopedic devices, G, wheelchairs, H, acupuncture, I is chiropractic care, J is counseling or psychotherapy. K is other things like horse or equine therapy and music, and then L is not using any treatment to help manage the symptoms.

(04:03:56):

And as the answers come in, we see that some of the top things are these therapies that people are using such as physical therapy, occupational therapy, speech therapy, all just about getting similar amounts of response. It looks like school adaptations are fairly frequent. A lot of people are reporting dietary changes, and a lot of people have also chosen other, so other types of therapy. No one yet for acupuncture and just a little bit for chiropractic care, and some folks are using counseling or psychotherapy.

Heidi Wallis (04:04:39):

I think this really lines up with the symptoms that we talked about in the morning of speech and fine motor issues being common across all of the CCDS.

Larry Bauer, RN, MA (04:04:52):

Yes, absolutely. Absolutely. Okay. Well thank you everyone for responding to this. I'd like to now turn to our panelists that have joined us live today. Welcome. We're so glad that you could be here with us. I was wondering, Gina, as you saw these questions about types of treatments that you're using, would you like to share anything about current or past treatment regimen?

Gina Nichols (04:05:25):

Absolutely. So my name is Gina. I'm located in Iowa, and I am the parent of Carter who has CTD. He is 16 years old now. Carter was diagnosed when he was eight. So when you see a list like that pop up, you're like, oh, I forgot I did that. Oh, we did do that. It's because of the path for some of us to diagnosis was a lot longer. So the things that we may have tried early on or have done really intensively. He started physical therapy when he was 14 months old. We had occupational therapy in house when he was less than 20 months old. So those started off very early, long before we even had a diagnosis except for our lovely failure to thrive that many of us got at the very beginning there. So we spent many times and many days and months in therapy offices throughout those early years until we got into school moreso and accepted those therapies as part of that school day as well, to keep things, trying to have a family life still at the same time, to balance all of those aspects.

Larry Bauer, RN, MA (04:06:31):

Okay, thanks Gina. Just before we go on, I just want to remind folks that they can also be calling in today. The telephone number to call in is (703) 844-3231. Once again, (703) 844-3231. And if you call in, you'll be put into a queue and we will try to get to as many callers as possible. Regina, good afternoon. Regina, would you like to respond to this as we're talking about treatments and both medical as well as non-medical approaches to treating CCDS?

Regina Bogar (04:07:15):

Yes, thanks, Larry. My name is Regina. I'm in Oklahoma. I am the mother to Chelsea, who is 28, soon to be 29, and I am also the Grammy to Caden, nine years old, who is Chelsea's son. So to piggyback what Gina just said, it's a little bit different of a journey whenever you have a late in life diagnosis. Chelsea and Caden were diagnosed simultaneously through Caden's journey. Chelsea went undiagnosed until she was 23 years old. Looking back into her childhood, we see that we did have some struggles, as you've also heard through the morning session and through the scientist explanation of CTD, it does present differently in females and males, and so it's a bit different presentation and journey for each of my loved ones. Chelsea doesn't really have much intervention as a child. She did struggle in school and we did receive some academic supports in her education beginning in third grade.

(04:08:13):

However, back then it was a totally different journey in the school community as well with diagnosises and lack of diagnosis. And so there were barriers to her receiving any kind of interventions. For Caden, we caught on pretty early in life when he was an infant that he was struggling with, of course, what all the others have shared, failure to thrive. He had early onset with seizures. He actually did not move

much in utero during Chelsea's high-risk pregnancy and had a complicated delivery. He was born with torticollis, so we did start physical therapy first and foremost to help with that torticollis journey. And while in that early intervention physical therapy, they were able to use their trained professional eyes to see that he also was struggling with occupational needs as far as gross motor skills and physical abilities to do things such as reaching out for toys.

(04:09:11):

He wasn't doing any of that. He missed all of his milestones, wasn't babbling, so we were able to get into early speech therapies, and he's pretty much lived his entire life from four months of age through nine in therapies. He does receive speech, occupational, physical. He receives behavioral therapies. We use medication management for the behaviors and anxieties. He receives supports through education. He's in a special education blended learning with SPED classroom as well as some gen ed immersion. And even as far as going to church on Sundays, he's in a blended environment there. He has a special education religious worship center facility as well, so he has quite a bit of extensive therapy interventions.

Larry Bauer, RN, MA (04:10:00):

Okay, thanks. And I was wondering, how does Caden do with these treatments and therapy? So when he goes to PT, OT sessions, is he cooperative? Is it a struggle

Regina Bogar (04:10:10):

Because he's lived his whole life through it, he has had significant gains. He's made great progress with it. I think that the key there is that it was a very early intervention, though CTD doesn't currently have a treatment, we are finding that the benefit of early detection, early intervention and getting him to those resources quickly has been a significant gain and bonus for him. Again, because he has been in it his whole life, he's also burned out on it. And so we see a lot of the behavioral aspects of therapeutic burnout. He has to come out of school twice a week on Mondays and Thursdays. He leaves school early.

(04:10:51):

He's only in school for a few hours, so he misses out on his academics as well to attend these services. These are his private services. While he's in school, he's also pulled away from his peers in the academic setting to go in and receive school-based services. And so sometimes that can create issues whenever his desires and his wants are to be along his able-bodied peers in the classroom environment, doing whatever activity they're doing, hands-on education, and he's having to come out to go do something by his self just to learn to communicate or just to learn a little bit more social emotional skills or physical skills to grasp the pencil while everybody else is doing their academics. So it can be a bonus, but it definitely comes with its struggles as well for him.

Larry Bauer, RN, MA (04:11:35):

Thank you. Christina, would you like to share anything about current or past treatments?

Christina Sawaged (04:11:44):

Yes. My name's Christina. I'm from New Jersey. I have two children with GAMT, Eliana, who's four, and Luca, who is about to be two. They were both diagnosed in November. Eliana, we always knew something was different about Eliana and we could never figure it out. She was late hitting her milestones. At two, she was still not speaking, so we put her into speech therapy. She had early

intervention coming to the home. And then at three, she qualified for the public school system. She's in a self-contained class with children just like her, although there's no other children with this. At this time, we still didn't have a diagnosis. And then they also added physical therapy and occupational therapy. Eliana has a very weak core, weak low muscle tone. She has a hard time walking long distances. And her teacher, they've told us they're going to hold her back in going to kindergarten. She's very academically delayed.

(04:12:35):

She does speak, but not at a four year old's level. She mostly imitates what you're saying. So then Luca comes along, my son, who's just about to be two, and he was hitting all of his milestones as well. And then at 13 months, he started having seizures. So it took us until he was 18 months old to get into a neurologist around here, because that's how long it takes. And then we started genetic testing him, and that's when the GAMT showed up. And then they said, you need a genetic test to your other child. And that's when it also showed up at Eliana. So Luca has seizures. He also has something called PPP3CA deficiency, and we don't know how that's reacting with the GAMT. Eliana has abnormal EEGs. She has not presented with seizures yet, but neurology keeps telling me either coming, she has a lot of abnormal firing in her brain.

(04:13:26):

They can't medicate because they don't know how it's going to present itself, if it's going to be the same as his or different. And Luca receives occupational therapy, physical therapy, and developmental intervention in the home. He is completely non-verbal. Treatment is very difficult. Neither of them are responding well, and we're actually now going down the G-tube route. They vomited up constantly. It's a lot of medication, as all the parents know. Eliana, it has affected her behaviorally. She screams and bites and hits and cries so much she actually burst the blood vessels in her face. The advice I was given was to take a break from the... It's really the ornithine that's the problem. Take a break and start again. But it's like every time we do that, repeating the same cycle, Luca either spits out 75% of it or vomits it. So it's constant. It's just really challenging.

(04:14:21):

And so a G tube route is not easy either. But Luca is really in that prime mental development. And Eliana, still, she's young, but we can really see her delays now. The gap, her intellectual disabilities, the gap is getting bigger and bigger because she is four being diagnosed, whereas Luca's two, so he still has a little more time to get some of that treatment in. And I'm worried that if they don't start taking it orally, I don't know what's going to happen because really we don't know what's going to happen. So we meet with gastro next month to pursue the G tubes.

Larry Bauer, RN, MA (04:14:55):

Okay. And with Luca, is he receiving treatment for the seizures?

Christina Sawaged (04:15:00):

Yes. He takes medication for absence seizures. He takes that twice a day, and we've already had to up it twice. Although it is working, they're not completely gone. But before he started treatment, he was having seven seizures an hour.

Larry Bauer, RN, MA (04:15:13):

Okay. So he is having a response, not a full response, but some improvement with it. Okay. Because I think that's one of the other things we heard earlier is that the seizures can be difficult and challenging to treat. So thank you. I'd like to go to a telephone caller. I see that we have Celeste from North Carolina who's called in. Celeste, are you there?

Regina Bogar (04:15:37):

Hey. Yes, I'm here.

Larry Bauer, RN, MA (04:15:39):

Yeah. Celeste, what would you like to share with us about treatments?

Regina Bogar (04:15:48):

So there's nothing for CTD. We tried the supplementation with Levi a couple different rounds and never saw any improvement. And so we stopped those. But I wanted to speak mainly on medication-

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Regina Bogar (04:16:03):

And so we stopped those. But I wanted to speak mainly on medications and therapies. He's on a significant amount of medication in order just to maintain generally manageable behaviors and it's very remarkably different if he weren't on that medication at all. Working with his developmental pediatrician, we try a variety of medications to combat his symptoms such as impulsivity, aggression, emotional regulation. Sometimes they work and sometimes they don't. We often find ourselves having to circle back and retry medications or play with the dosing in order to see something for a temporal amount of time. So we're starting to see cycles. So we'll find a regimen that works and then eventually it'll plateau and we have to go back to the drawing board. And the doctor often says somebody who didn't know Levi would look at this medication list, they would think I was crazy with the dosing and all of that.

(04:17:09):

But it's just crazy how, I don't know if it has to do with metabolizing or also with the growth. But whenever we have to go back and do the medication management, it's difficult especially as he's getting older and stronger. So his self injurious behaviors, aggression and screaming take a toll, but then also going limp, eloping and his extreme impulsivity. So we find ourselves having to think outside of the box. His developmental ped has tried pretty much everything but the kitchen sink to look at meds that will help reduce his behaviors and increase his mood and focus. On top of that, he's also participated in multiple therapies. We've done ABA, occupational therapy, speech and hippotherapy. Progress really depends on the day, but it also depends on the therapist, their personality and their expectations. So whenever everything plateaus, it's always a struggle. The struggles increase and then it's a dash to find the next dosing or the next med or the next therapy to help things calm down and to get it back to manageable.

Larry Bauer, RN, MA (04:18:24):

Yeah. Celeste, can you remind us how old Levi is?

Regina Bogar (04:18:27):

So he's 10, he'll be 11 in April.

Larry Bauer, RN, MA (04:18:29):

He'll be 10. Wow, okay. From all that you described, I thought he was going to be older than that. But okay, so he is just 10 years old. Okay, thank you very much. And next we also have Britney from Minnesota on the phone who's the mom to a child with CTD? Britney, can you join us?

Brittany (04:18:53):

Hi, yes. Thanks for having me back again. I feel like the previous person who called in was a good kind of segue to what I wanted to speak about with the potential medicine for behaviors and things like that. I think kind of going on off what I said previously in relation to this because my son and several of our children have prolonged QT. There's this very long growing list of medications that they are not able to take and several of those are for things like ADHD or hyperactivity. And those are just things that would interact poorly with his condition of prolonged QT. So that's unfortunately something that is a concern for us in the future. My son is three and so right now we're starting to see some of those emerging behaviors that are mild. But I think as he continues to grow and then into puberty, not being able to manage those behaviors because of his other heart condition is also very scary. So that's been a concern for us.

(04:20:02):

And going back though to and other things like he can't be on arginine because of its interaction with the beta blocker. That was potentially why he went into that hypoglycemic event last month. So those are some of the medical interactions and some of those concerns are if we can find a therapy or treatment we don't have to maybe worry about in the future.

(04:20:28):

But going back to therapies piece, my son's in basically everything that you saw on the tab there. He started with SMOs when he was 10 months old pre-diagnosis or pre D-day as some of us like to say. And he wasn't walking. He didn't walk until he was just at 18 months. He was basically that kid who hit every milestone right before it was outside of the norm. But now he's in AFOs and we're very happy that he is as we feel like they help at least give him the balance, and for him he feels more stable wearing them. And then we're really blessed to be in a school system that he is able to go to daycare and he's pulled from daycare within that system to go to do PT speech and OT. So his dad and I are able to work full-time jobs at least right now while he gets the care he needs. So we're very lucky and blessed for that with that.

Larry Bauer, RN, MA (04:21:33):

Okay. Well thank you. Thanks Britney for calling back. Heidi, I was wondering if we received any written comments related to treatments

Heidi Wallis (04:21:41):

We do. On the topic of treatment successes. We have a comment from Becky in Utah whose son has GAMT. She says, "My child lives a pretty normal life since he was screened at birth and started treatment right away. He does not show any signs of GAMT. We are so thankful for the newborn screening." So

definitely a treatment success there. Jennifer in California shares, "It is heart heartbreaking to get my grandson's diagnosis as not much hope for his development was offered. But watching him gain skills through extensive behavioral therapy has been heartwarming and he has an ever-growing vocabulary and amazes me with his increasingly developing skills in most developmental areas." And then finally, Amy in Australia has a child with GAMT and also shares, "My daughter was picked up on newborn screening with GAMT in Australia and started treatment at six weeks of age. And we have been able to keep her GAA levels consistently around five. We treat four times a day with creatine, ornithine and sodium benzoate and follow a restricted protein diet. And we would love there to be progression with treatment options as well."

Larry Bauer, RN, MA (04:23:03):

Okay, thank you. Thanks. Okay. I'd like to move to another polling question. If you could take out your phones again and go to pollev.com/ccds. The next polling question is going to have it continues to be about treatments and about how well the treatments are working. So the question states, "How well does your current treatment regimen treat the most significant symptoms of CCDS? A is not at all, B, very little, C, somewhat, D, to a great extent and E, not applicable because we are not using anything. In this case we're we're asking that you just choose one of these responses. And as the responses come in, it looks like somewhat is getting almost 50% of the responses. And unfortunately very little and not at all are also getting a significant number of responses. But only about 13, 15% are to a great extent.

(04:24:20):

And once again, we put this question in not applicable because we're not using anything and it seems like everyone with this condition is using something, so that's been consistent. And as the response levels slow down, it looks like, yeah, it's almost half say very little and just about a third are saying somewhat. So I think this is a statement that we've been hearing today about the unmet medical need within the CCDS community.

Heidi Wallis (04:24:54):

Definitely.

Larry Bauer, RN, MA (04:24:55):

Yeah. Okay. Well thank you. If we could go back to our Zoom panel for a minute. I'd like to ask Beth. Beth, can you respond to this about what are treatments working? Are they not working? How well are they working?

Beth Robinson (04:25:15):

Okay, I am Beth from Missouri and I have a 28 year old son who has GAMT. He is one that was diagnosed with pyruvate dehydrogenase deficiency at 14 months old, which is all protein. And from that treatment, he made gains but not necessarily intellectually. Physically, he started walking and he could speak. At 12, he was diagnosed with GAMT. And I will say that I was kind of tentative like, "Well, how's this going to help?" Was hopeful and did not see a lot of gains with the treatment of creatine and ornithine. But then I will say about seven years later, he developed behaviors that I found out that if not treating him as the true GAMT saying low protein, creatine, ornithine, that caused I think a lot of the aggressive behaviors, anxiety, those type of things. So now he is on high doses of creatine and ornithine.

(04:26:23):

In the morning is where we see a lot of his behaviors. And I think that's because he's been without any kind of supplementation all night and he wakes up in the morning and needs something. So when we talk about some kind of treatment, it would be good to have some kind of a long lasting something that stays in their system is what I see. I will say I use a lot of supplements so far as B6, taurine, just the different amino acids that calm him and they have worked. And so I think that there's some neurological aspect of this lack of creatine affecting other systems in their bodies that we don't really understand. At least that's what I'm seeing in my son.

Larry Bauer, RN, MA (04:27:12):

Okay, thanks Beth. And your son is one of the older people that we've heard about today. We've heard about some younger kids. I'm just wondering how has the dosages changed over time? So has he been on pretty stable doses as he's gotten older? Have you need to increase, decrease because of side effects? How's that played out for you?

Beth Robinson (04:27:37):

Well, because the doctor that follows him has never seen a patient that has what Josh has, I've learned a lot from this community and totally upped his dosage and then saw a lot of improvement from that. I've heard other people say he will throw it up sometimes and that is very disheartening because of just like a gag reflex and it just comes back up.

Larry Bauer, RN, MA (04:28:06):

Oh boy.

Beth Robinson (04:28:07):

So that would be a great thing if it could have a better taste so these patients, children could tolerate it so it can help them. But yes, he is at a high dosage right now and I am seeing some benefit from that.

Larry Bauer, RN, MA (04:28:23):

Okay, thank you. And Dan, we haven't heard from Dan yet. Dan, would you have anything you'd like to share about treatment, successes, maybe challenges with treatments?

Dan Coller (04:28:35):

Hi, my name's Dan. I'm from San Diego and I have a seven year old son, Cadman with CTD. We're pretty fortunate in that Cadman doesn't suffer from the seizures or aggressive behaviors that we've heard about today. The challenge with the treatments is really knowing if anything's working. We can look at him and judge behaviors whether there's some improvement or not. But it's very challenging to know whether it's his therapies or the supplements that we do use are doing anything. His medical team does regular blood and urine tests to look for ratios of creatine, creatinine. But I mean he has had MRSs done to see if there's any creatine getting through from the supplementation we do. The challenge with that is going under general anesthetic requires you don't eat. So we're not sure. The timing is challenging.

(04:29:48):

But we have an attitude of we give him everything. We have no idea if it's doing anything at all. It is a challenge. It's four or five times a day of getting him to take the supplements we're giving him. And fortunately he takes them pretty well so we're lucky there. But I'd say knowing that identifying any

treatments that are out there and then being able to track is this working would be a huge relief to know that the effort that we're doing is actually doing something.

Larry Bauer, RN, MA (04:30:27):

And Dan, how old was Cadman when he was diagnosed and do you have other children or other relatives that might have CTD or how did he get diagnosed and at what age?

Dan Coller (04:30:42):

It was shortly before he was two and it was through a full genetic test that he was diagnosed that we pushed for to get that test done. It was a-

Larry Bauer, RN, MA (04:30:55):

Why did you push for full genetic testing?

Dan Coller (04:30:58):

Just every other diagnosis we were getting was not coming up with anything. The failure to thrive, he had very low muscle tone, he was missing a lot of the goals. The milestones he was supposed to be making, he was behind on. And fortunately where we live, we have a lot of good hospitals and doctors nearby. So we were very fortunate with that. But since he got tested, it's been full every therapy that we can find, every supplement that's out there. Again, we're very fortunate. He did have a seizure, which was I guess our sort of moment of this is bigger than he's just a little bit behind, and was on Keppra for a number of years. But through, I'm not sure how many, several overnight visits at the hospital where they were doing scans and ones at home, they felt that he could come off that which he did. And we are 99% sure he's not having any seizures.

(04:32:21):

But one other thing I'd come back to is the treatment of CTD specifically is very challenging because it manifests so much with the communication. So it's clear to me that Cadman will understand things. "Hey, if you do this, you'll get a treat," or, "Go give this to your sister," or, "Go put this in the kitchen." He'll recognize that. But he has almost no communication coming out of him. And so knowing if medication's making him feel strange, upset his stomach, any of those things, it's just so hard. And I was looking at the list of treatments that you could do and I was looking at acupuncture and I was just like how would I explain to this guy that we're going to stick him with a bunch of needles? And it different.

Larry Bauer, RN, MA (04:33:20):

Right.

Dan Coller (04:33:20):

It was just no way. There's just no way.

Larry Bauer, RN, MA (04:33:25):

Yeah. When we came up with the list, we tried to put everything. We actually had CBD on there but took it off the list.

Dan Coller (04:33:33):

It's not that it was a bad question, it just made [inaudible 04:33:35] into there are things that we can't do that they may have an intellectual capability of, but they can't communicate. Right. Communication is such a heavy thing on this.

Larry Bauer, RN, MA (04:33:51):

Yeah. I've been very impressed today with the consistency of that report across the board from people and the challenges that has caused within families. So yeah. Yeah, Regina.

Regina Bogar (04:34:07):

Larry, you giggle about the CBD and almost doing that on there. But I will say that Caden has been on CBD for many years. We first went on it for seizure control because he had a very bad response to the Keppra and the antiepileptics. And so at his neurologist's suggestion, we ventured into that. And so he has been taking that since 2018 and it has well controlled his seizures to the point that he went from having multiple daily seizures to being able to come off of the seizure medication. And then only in the last year has he been put back on it because he is showing nighttime activity, which of course is a high risk for SUDEP.

(04:34:47):

But the very first thing we noticed when he took CBD oil for his seizure disorder is that he finally began to play with other kids. So in occupational therapy, we were literally teaching him how to play with other peers and he would stand off several feet away and watch out of the corner of his eye, but he would not engage them. After taking CBD oil, he would turn to them and actually smile at what they were doing. He finally started smiling and engaging with peers. And so it's interesting that you said that and that you almost included that because there are different modalities that can and should be explored.

Larry Bauer, RN, MA (04:35:28):

So how old was Caden? He's nine now, right?

Regina Bogar (04:35:31):

Yes.

Larry Bauer, RN, MA (04:35:38):

How old was he when he started the CBD? Just recent-

Regina Bogar (04:35:42):

No, he started in 2018.

Larry Bauer, RN, MA (04:35:42):

With CBD?

Regina Bogar (04:35:42):

December '17, yes.

Larry Bauer, RN, MA (04:35:45):

Wow. So he was little.

Regina Bogar (04:35:46):

He was little. He was very little. And we do talk very frequently. Every six months we do liver enzyme panels and stuff just because there's no good literature. And again, this goes into the unknowns that we were talking about this morning in this morning sessions. We don't really know and so in many ways we are the guinea pigs. But we had tried so many other things that he had had adverse reactions to that were far scarier than the unknowns because we could see what was happening and that just was not okay. And so yeah, we talk and work closely with his entire medical team and we asked them to draw those panels to kind of watch those liver enzymes because we do know that it metabolizes in the liver.

Larry Bauer, RN, MA (04:36:28):

And was it challenging to find an appropriate dose for a child that young? I mean, did you have to experiment or how did they... I'm just curious.

Regina Bogar (04:36:37):

Yeah, so his neurologist actually is the one that doses him and they kind of went off of their base what they were looking for in milligrams, how many milligrams they wanted him to have each day, and then what his stomach could tolerate. Because again, you don't really know. And so as they tapered up, it did cause some irritability in his bowels which we already struggle with. And so in a way it was like, oh, yay, we finally have progress. But it wasn't for the right reason. And so they tapered back down to where he wasn't having any adverse reactions from the digestive area.

Larry Bauer, RN, MA (04:37:12):

Okay. Well thanks. I'm glad you shared that. I'd like to go to a telephone caller now. We have Jolene from California who has a child with CTD. Jolene, are you with us?

Jolene (04:37:26):

Hello, yes.

Larry Bauer, RN, MA (04:37:28):

Go ahead, Jolene. What is it that you'd like to share about?

Jolene (04:37:33):

In the area of treatments, similar to Cadman, we tried supplements for my son who has CTD and really didn't see any impact from using them. And the thing that's had the most impact, although I'd still call it minimal, is really intensive ABA therapy. But even with that, we still are desperately in need of an effective treatment for a CTD that could make a more significant impact. And one other thing I don't know has been raised yet is a fear of doctors. I think after all of the medical treatment and testing and procedures and multiple surgeries my son has had, he's terrified of doctors, doctors offices. And if he sees a white coat, he starts screaming and shows a real fear. He fears for his life when he sees a white coat.

Larry Bauer, RN, MA (04:38:27):

Yeah. Thanks for sharing that, Jolene. We've heard some things about behavioral outbursts and things, but you're the first person that's actually talked about some of that as a side effect, anxiety as a side effect. It sounds like the kids have to go to so many different treatments. We've seen images of the kids having to be hooked up to EEG machines and going through surgeries and stuff. So it's understandable that developing anxiety could be a side effect from that. So thanks for sharing that. Dan raised his hand. Dan, would you like to share?

Dan Coller (04:39:04):

Yeah, just going back to that supplements topic that was just brought up again. I mean, I think a lot of us who do give the CTD patients supplements do it because we're kind of afraid not to do it right. There's no evidence that it does anything. And I would agree that the improvements that we see are probably pretty consistent with how much ABA therapy he's getting. I mean, we saw anecdotal evidence of him improving with, just I guess going against the intellectual disability, but when we changed supplements or made them more intense. But it was also the same time when Covid was over and he was back in school. So anything that could be done to either quantify, yes, these treatments work or doing something would be, I think, very beneficial even just to the psychological wellbeing of the caregivers and hopefully, obviously doing something for the patient themselves. And obviously the real goal is to find anything that's out there that can increase the creatine in the brain for the CTD community, we see that there are at least some treatments for the other CCDSs.

Larry Bauer, RN, MA (04:40:48):

Okay. Thanks for sharing that. Heidi, do we have any written comments that have come in?

Heidi Wallis (04:40:53):

We do. So on the topic of treatment failures and downsides, we talked about the successes. We've got a comment from Laura in Washington and she comments, "I was told by someone that develops drugs that I'm expecting too much to see us getting treatments soon because CTD is a new condition, but CTD was discovered more than 20 years ago," and she feels that that's unacceptable and hopes for better for her child. And then I've got two comments from GAMT caregivers. I've got a comment from Anthony in Australia who comments that, "Current treatment for GAMT involves a large volume of powders consumed several times a day, struggling to give a child just five milliliters of medicine is something most parents can relate to. Now consider giving 10 to 20 times that amount. We currently give 70 milliliters of a bitter tasting powder and having to do this five times a day every day, including at school, as my daughter grows, the volume will only increase."

(04:42:07):

And then last on a similar topic, Jenny from Connecticut commented about her sons with GAMT. She said, "We keep feeding them their daily cocktail three times a day of creatine, ornithine, and sodium benzoate. It's a terrible tasting mix. And I watch my sons gag and sometimes throw it up. Sometimes they run away and hide so they don't have to take it. It's frustrating as a parent and sometimes I just want to give up and let them skip the dose, but I can't because I know that if I skip, then I'm just allowing more brain damage to occur." So definitely parents feeling pulled in many directions to tackle these difficult treatments or just to find any treatment that they think will help.

Larry Bauer, RN, MA (04:42:56):

Yeah. Yeah. Two themes that keep coming up are the sheer quantity of medication that kids have to take and then the formulations that nobody has come up with a way to mask the taste of these things yet. We've heard that consistently.

(04:43:17):

Okay. I'd like to go to another polling question. If you can open up pollev.com/ccds. This question is what are the biggest drawbacks of the person with CCDS' current treatment approaches? Select up to three. A, is it they're not very effective at treating target symptoms. B, they only treat some but not all symptoms. C, is the high cost or copay which is not covered by insurance. D, is limited availability or accessibility. E, is medication side effects. F, is that they require too much effort and/ or time commitment. G, is long-term safety concerns. H, is other. And I, is not applicable because we're not using any treatments. So once again, these are the biggest drawbacks for the person with CCDS' current treatment approaches.

(04:44:25):

Unfortunately, the one that's getting the greatest percentage of answers is not very effective at treating target symptoms. We've heard several times throughout the day that there still are no FDA approved treatments for any of the CCDS conditions. Another one that's getting a lot of attention here is that requires too much effort and/or time commitment, as we've heard about administering these powders. Another one is that they treat some but not all symptoms, which indicates that for these conditions, there still are no disease modifying treatments that actually treat every aspect of the disease. High cost or copay and not covered by insurance also has gotten a lot of responses. And that's not a surprise knowing that these supplements, they're not approved for these conditions or they're not indicated for these conditions. Some folks have long-term safety concerns. And there's some issues with availability and side effects for the medications. But clearly on top is the not effective at treating the target symptoms, which is unfortunate.

(04:45:51):

Okay. Well, thank you everyone. If we could go back to our Zoom callers. Can I ask? Does anyone have anything they would like to say about this, about the downsides of treatments? If you could raise your hand? Dan, go ahead.

Dan Coller (04:46:10):

I mean, the first thing is that there aren't any for CTD. So everything that we're doing as far as, I guess, medical intervention, not therapeutic intervention, we're throwing mud at a wall and hoping it sticks. We have non idea what's helping or not. So again, being able to quantify if anything's working on the medical front or getting proof that something does would be the key. And then as far as treatment of the symptoms with all the therapies, I can only speak to life in California. Fortunately, we live in a place where the state helps out a lot. We do have pretty good medical insurance. But I mean, it's almost a full-time job for someone to manage getting them. We face the issue actually right now with a lot of the sort of therapist companies that we're going through are struggling to find employees, which I know a lot of industries are, but I'll let someone else chime in.

Larry Bauer, RN, MA (04:47:24):

Yeah, Christina, I saw your hand up.

Christina Sawaged (04:47:29):

Yeah, I agree with Dan. New Jersey has reputation for having a very difficult disability system, so it's like they hide disability benefits from the family. So it's like you're digging crazy to get them. And they make it almost like the kids are not eligible and make it very difficult. But treatment with Eliana, I sometimes wonder like the psychological damage going on. Because yes, she's on the younger end for treatment and we don't know where she's going to be when she's 20. We know she's going to have developmental delays, but the treatment-

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Christina Sawaged (04:48:03):

... mental delays, but the treatment has completely impacted her life. And that is the struggle right now. And even children diagnosed at newborn are still going to go through the same treatment with GAMT. So yeah, they'll be used from the time they're born. But even when I speak to the parents who have teenagers with it, they're still struggling. Eliana wakes up in the morning and doesn't say, "Hi, mommy." She says, "No medicine. No medicine." And then she must say it to me 30 times before she even takes her first dose. And it has basically consumed her life. And I'm like, "Is it going to be like this forever? And what's it going to do to her?" That's really been a struggle too. I mean the medication, it's horrible. And I taste every dose I mix and I'm like, "This is disgusting. No wonder she doesn't want it."

(04:48:44):

And going back to the caller, the fear of doctors. She's getting blood work drawn almost every month because the levels, both of them are all over the place. Constant EEGs. They're getting MRIs twice a year right now. The metabolics, geneticists, neurology, neurodevelopmental pediatricians, it is more than a full-time job just to get them to all these appointments. That is what's so crazy and it's so hard to get them to these specialists. It's crazy. Really. It's amazing that our kids have a diagnosis because some kids will go forever not having one. But it is not an easy life having a diagnosis, living with it.

Larry Bauer, RN, MA (04:49:20):

Okay, thank you, Christina. Regina, we'll come back in just a minute. We have one last polling question I would also like to finish during the meeting today. If we could bring up the next question? And if everybody could go to pollev.com/ccds. This question is short of a complete cure. What top three specific things would you want in an ideal treatment for CCDS? And for this question, please select your top three. A is easier administration, improved taste. B is fewer, no side effects. C is improved speech and communication. D is help with intellectual disability. E is better focus and attention. F is decreased seizures. G is better toileting and self-care behaviors. H, improved growth or fine motor skills. I is improved social interactions. J is better behavioral control. K is greater independence and daily activities and L is other.

(04:50:25):

So like I said, you can select up to your top three things you'd like to see short of a complete cure, but in an ideal new treatment for CCDS. And the front runner is C, improved speech and communication with a close second with help with intellectual disability. It looks like people would actually like ... at least some people would like to see each of these things as a possible new treatment, greater independence and daily activity, better behavioral control are up there. Toileting and self-care behaviors, help with that. Better seizure control, fewer side effects, but it looks like C and D as we get more responses are pretty

closely tied for first. So improved speech and communication and help with intellectual disabilities seem to be the top two responses that we've heard.

(04:51:28):

So thank you everyone for participating in that. I just would like to go back to the Zoom panel. And Regina, we've shifted gears a bit. Do you still want to respond to this? What would you like to see in an ideal new treatment for CTD, especially in your family?

Regina Bogar (04:51:49):

You know Larry, I would have to say based on this list, under the other category, accessibility and affordability. A treatment doesn't always mean that it's accessible to you. And sometimes that treatment, especially with us being a rare disease population, what do those centers look like? Where do we have to go? How much work do we have to miss? How frequent do we have to be there? What is the route of administration? Is it something that's sustainable? Many of these panelists and parents and caretakers are sharing today, there's so much complexity that goes with that question that I think we could probably go on all day on it. But accessibility and affordability I think for our family would be the two most significant barriers or factors to what we would consider a treatment.

Larry Bauer, RN, MA (04:52:35):

Yeah, I hear that. Numerous people have talked about that they have turned to using G tubes for treatment. That's not a benign way to take medication, having to have a G-tube. So thanks, Regina. Anyone else on the panel would like to respond to this? Beth, I saw your hand go up next.

Beth Robinson (04:52:56):

So I think answering this last question, it depended on probably where you are in the journey and how old your child is. If I had a young child, I would have answered probably different. But now-

Larry Bauer, RN, MA (04:53:10):

Your son's 28. What would be-

Beth Robinson (04:53:12):

My son is 28.

Larry Bauer, RN, MA (04:53:13):

So what would you like to see?

Beth Robinson (04:53:14):

[inaudible 04:53:13] Looking For him to have social interactions with the people that he already knows that are meaningful and to be able to control his behavior so that people are comfortable around him. Whereas if I was having this discussion when he was four or five, I would say I want his intellectual abilities to be higher. So I do think we would want all of these things that you have listed with a better treatment.

Larry Bauer, RN, MA (04:53:42):

Okay, thanks Beth. And Gina, we just have another minute for the Zoom panel. Would you like to add to this conversation?

Gina Nichols (04:53:50):

The only thing I really wanted to add is that these things are so linked. They're interdependent on each other. So even when you get advances in one area, you may go back again and regress because you have seizures that have happened. So skills that are gained may be lost because of something else is occurring. That's what happened with speech for us. We lost all of our speech because seizures got worse. So the linkage between all of those things come in are very important for the progress our kids make, the treatment.

Larry Bauer, RN, MA (04:54:21):

Okay. Well, thank you. Thanks, Regina, Gina, Dan, Beth and Christina for being with us today and participating live and being willing to be put on the spot. We really appreciate it. And thanks and all the best to all of you. I see that we have a phone call coming in from Kim in California who has a child with GAMT. Kim, are you there?

Jolene (04:54:48):

Hi there, how are you?

Larry Bauer, RN, MA (04:54:50):

I'm doing well, Kim.

Jolene (04:54:50):

Thanks for having us today.

Larry Bauer, RN, MA (04:54:55):

Kim, do you have something you'd like to say about your hopes for the future for new treatments?

Jolene (04:55:01):

Sure. I have two kids with GAMT. My son was diagnosed at 10 months old and he's now 17, and my daughter was diagnosed at birth and she's very typical. And what I just wanted to mention about treatment is that even with treatment from a really early age of 10 months old, it was just a few years ago that we discovered that my son was having up to 100 absence seizures a day and he's been on treatment for years and years. And it really came as a surprise to us. And although there have been difficulties with a lot of things, seizures was one I thought that we had escaped. And so now our EEGs are constant and all the time. And so I hope that with the future of treatment we would be able to control that without having to use anti-seizure medicines. And the things are still difficult even though he was treated from 10 months old. Self-care is definitely one of them. Having fine motor skills, he can't brush his teeth or wash his hair, wash his own face or shave. Everything is difficult for him. Nothing comes naturally or easily. Yeah.

Larry Bauer, RN, MA (04:56:20):

Okay. Thank you. Thanks so much, Kim. Heidi, do we have any written comments that people have written in on this topic?

Heidi Wallis (04:56:27):

We do. I have some comments about hopes for future treatment and treatment goals. And Michael and Virginia commented, "I would love to see my son one day be able to hold a pen properly, write his name, call my name, and open a discussion with his sister and ride a bike or shoot a basketball." Beth in Missouri comments, "A treatment for anxious behavior that causes aggression would be greatly appreciated. I hear that a lot in the GAMT community that sometimes when you do finally get that treatment, it's difficult to give to your child."

(04:57:13):

You see a lot of these behaviors emerge whether it's a result of finally getting the creatine or like Christina mentioned, it can be a result of that struggle with the parent and the difficulty of this treatment. So the anxiousness is an issue with a lot of our kids. Abir in the United Kingdom mentions that he would like to see his son with CTD thriving and holding a pen and writing his name down and focused and able to read a book. When he is asked to be able to say his dad's name, he'd like him to be able to say it and also to be able to say how old he is. And so some really ... probably other parents would think basic things. I think our community would consider pretty big victories with treatment.

Larry Bauer, RN, MA (04:58:12):

Thank you. And we also have a caller, Randy from California who has a child with CTD. Randy, are you there?

Randy (04:58:24):

Hey Larry, Heidi. Yeah. I got a five-year-old with CTD and just kind of share a lot of stuff even Christina and Dan shared. To be up to speed with the treatments, you got to be a junior chemist and know how to weigh stuff out. You have to be consistent with delivering it, and at the same time, you don't know if it works or not. So it takes a full commitment from families, obviously from our kiddo and then you have to go arm wrestle insurance. So it is challenging. So when it comes to hope for the future, something that everybody in all walks of life and every state can really take advantage of and that do treat some of the biggest challenges we have, communication behaviors, seizures. To Heidi's recent point, a little bit of improvement goes a really long way for our kiddos and their families.

Larry Bauer, RN, MA (04:59:22):

Okay, thank you. Thank you so much. Well, that comes to the conclusion of hearing from our panelists and from folks on the phone. I apologize to anyone who was in the queue on the telephone that we did not get to. Please consider writing in your comment or you can write comments for 30 days after the meeting. So as we come to a close for today's meeting today, as your moderator, I want to say it's been my pleasure to hear the stories you'll all have shared today. It takes a lot of courage to share so deeply and we have all learned from listening from you.

(04:59:57):

Now, it's my great pleasure to introduce Dr. Sangeetha Iyer, who has the impossible task of presenting a summary of today's meeting. Dr. Iyer received her PhD in molecular pharmacology from the University of Pittsburgh and completed her post-doctoral research from the University of Texas at Austin. Since 2020,

Dr. Iyer has been working with the Association for Creatine Deficiencies as their scientific advisor to define their research initiatives and roadmap. She brings her expertise in working with rare disease patient groups, clinical key opinion leaders and drug discovery process to her role with the ACD. Dr. Iyer has been listening all day and will distill the meeting into some of the key takeaway learnings about CCDS. Dr. Iyer, over to you.

Sangeetha Iyer, PhD (05:00:46):

Thank you Larry for that kind introduction. It's my pleasure to be here today and as Larry said, I have the difficult task of summarizing everything we've heard today. I'm going to do my best and share at a high level everything that we've learned. Our session today was opened by Heidi Wallis, parent and executive director of the Association for Creatine Deficiencies. We then heard from Dr. Anna Choe from the FDA introducing the purpose of PFTD meetings. That is to provide insights from experts and caregivers of people living with cerebral creatine deficiency syndromes or CCDS to help facilitate treatment development and clinical trials for the same.

(05:01:28):

We then heard from Dr. Andreas Schulze, a physician researcher from the Hospital of Sick children in Toronto, Canada. He told us about the three types of CCDS, CTD, GAMT and AGAT, each of which is associated with a lack of creatine from birth due to defects arising from the genes. The clinical symptoms shared by some of these CCDS are overlapping. They're marked by developmental delays, hypotonia, seizures, and an overall failure to thrive. While GAMT and AGAT have supplementation options available, CTD has none. And while GAMT can be diagnosed at birth in certain states, AGAT and CTD currently do not have this option. And finally, CTD has the largest prevalence of the three CCDS disorders with hundreds of reported cases.

(05:02:20):

We then heard from a panel of caregivers who reported on CCDS symptoms and the daily impact of living with the disease. Whitney is parent of Reed, a 12-year-old with CTD. When he was younger, Reed suffered from failure to thrive, GI issues and cognitive impairments. After the age of two, he developed frequent seizures, lost the ability to swallow and had to be fed via a G-tube. In addition to the profound cognitive deficits, including lack of speech, Reed also developed behavioral problems of aggression and self-injury, making him a risk to himself and others around him.

(05:02:58):

We also heard from Kimberly, mom to 22-year-old Alison who was diagnosed with CTD at the age of 10. She was one of the first few females to be diagnosed with CTD, although that number has now increased. Today, as an adult female with CTD, even simple things such as toilet training or monthly menstrual cycles are overwhelming. Alison also does not understand the concept of social boundaries or mores and can be overly friendly with strangers. This places her in vulnerable situations, because of which she has to be watched closely at all times. In recent months, Alison's speech has shown further signs of impairment. She uses fewer words and is not as clear as before. Because the course of this disease is unknown, the future will continue to present many unforeseen challenges for their family.

(05:03:50):

Next, we heard from James. James is dad to Freddy, a six-year-old boy with CTD. Freddy was diagnosed at the age of two after many frustrating months of trying to understand why he had terrifying breath holding episodes that caused him to lose consciousness. He has since had frequent infections, chronic GI

issues, vomits frequently, all of which contribute to his reduced growth. Learning new tasks with limited cognitive skills and poor retention span is frustrating.

(05:04:22):

We then heard an uplifting account from Jenny. Jenny is mom to 20-year-old Christina. Christina was diagnosed with AGAT deficiency, the rarest of the CCDS disorders at the age of 10 months. Prior to her diagnosis, she had global developmental delay, hypotonia and failure to thrive. Following her diagnosis, she was lucky to be started on a regimen of creatine supplementation. Due to the timely diagnosis and supplementation, Christina quickly caught up on missed milestones and is a thriving young adult now.

(05:04:56):

Next, Jerry shared the story of two of his kids, Benny and Celia, who were diagnosed with GAMP deficiency on the same day. The difference being that Benny was six years old at the time of diagnosis while Celia was 13 months old. Once again due to timely diagnosis and supplementation, Celia is now a thriving 13 year old. Most days, her worries consist of trying to fit in and conceal the port of her G-tube, which is what separates her from her peers. On the other hand, the outcome for Benny has not been the same. He is now 18, supplementation has helped mitigate his seizures, but he remains nonverbal and reliant on his parents and family for care.

(05:05:40):

Glenda, another parent, shared that Carly, her 23-year-old was diagnosed with GAMT at the age of eight. Alongside intellectual disabilities, Carly started having seizures that were unmanageable with medication. Those years were very difficult for Glenda's growing family as Carly's siblings were deprived of many social opportunities due to Carly's unstable moods and the family's fear that she would hurt someone.

(05:06:05):

In summary, from the panel of caregivers in the first session, we heard that cerebral creatine deficiencies are marked by cognitive deficits, behavioral problems including regression, seizures, and an inability to live independently. We also heard from our live discussion and call ins that the impact of CCDS on seizure presentation was different. We also heard about pain sensitivity and heart abnormalities. Polls revealed that communication and toileting skills are chief concerns for CCDS families. While early diagnosis makes a world of a difference for GAMT and AGAT disorders where supplementation is able to mitigate some symptoms, taking supplementation presents a continuous challenge for them. Prognoses for individuals with these disorders remains unknown, so this presents an ongoing concern for most families.

(05:06:58):

Next, switching to session two. We received an overview of current CCDS treatments from Dr. Longo, a physician researcher at the University of Utah. We heard how for AGAT deficiency, supplementation with creatine if started under 10 months of age can result in neonormal development. For GAMT deficiency, supplementation with creatine, ornithine and sodium benzoate is recommended and when started early can prevent intellectual disabilities. However, impact after brain damage sets in is not good. For CTD, there are no known cures. Supplementation with creatine, arginine, and glycine is suggested. However, it's unclear if this provides any clinical benefit.

(05:07:48):

We then heard from a panel of caregivers on their experience with current CCDS treatments. Susie is mother to Daisy, a 21-year-old with GAMT deficiency. Daisy has profound intellectual disabilities, sleep disorders, seizure and behavioral problems. Her late diagnosis and the lack of availability of supplements

that could be easily administered have been a factor in the difficulties that their family has faced. Daisy's behavioral problems have been severe enough to necessitate extreme forms of intervention and the trauma that has been faced by Susie's family is immeasurable.

(05:08:28):

We also heard from two families where supplementation has successfully improved the living quality for their children. Leif and Miguel's oldest son, Max, was diagnosed with GAMT deficiency at the age of one. Supplementation was started early and consisted of creatine, ornithine, and sodium benzoate. This has helped greatly with symptom management, but even after so many years, it is difficult to stay compliant with it. Although Max has been taking supplements for a long time, he still hates how it tastes. He has to be watched to ensure that he's able to take all of it, and it can take up to 30 minutes to take it each time. This presents an ongoing challenge.

(05:09:08):

Christina, a 20-year-old with AGAT deficiency is grateful that she received an early diagnosis which enabled her parents to start her on creatine supplements. These have helped Christina regain her quality of life and thrive, but they are a constant reminder that she's different from her peers. The unknown future prognosis of this disease also underscored that there is a need for better drugs and dosage forms for CCDS.

(05:09:35):

Next, we heard from some families with CTD. Scarlet's mom shared her experience with CTD. For 13-year-old Scarlet, seizures have been the most difficult as Scarlet's family have watched her be hospitalized for days due to unrelenting seizures. Supplementation has failed to have any meaningful impact on her symptoms so she's mainly on seizure medication. Even so, the threat of breakthrough seizures remain. There are no drugs that are able to improve her cognition, speech, self-regulation, or social skills.

(05:10:08):

Similarly, Kayla and Sid are parents to four-year-old Crosby, who has CTD. Crosby had his first seizure right after his first birthday. Even with medication, he continued to have breakthrough seizures, which have required frequent dose adjustments. For their family, a treatment would mean not needing to give separate seizure medications for Crosby and having something that would actually help with his speech and intellectual disability.

(05:10:34):

Finally, Nathan shared how all three of his children, Elijah, Simon, and Ezra, have CTD. Intellectual disabilities aside, their most pressing concerns revolve around GI issues and seizure management. All three kids are on many different types of seizure medication, and Simon has additionally undergone surgery to manage his seizures. All three kids have a G-tube to help with nutrition. However, issues continue to persist as parents have to monitor the G-tube placement carefully at all times. For Nathan's family, an ideal treatment for CCDS would keep their children safe by preventing life-threatening seizures and the risky lack of weight gain.

(05:11:18):

In summary, we heard from CCDS families about how current therapies are a patchwork of seizure medication and supplements when available. Even with supplements have an impact, they are not easy to administer or take. For CTD, there are no options with proven efficacy. Seizure medications work for

some but not for others. Palliative therapies such as speech, occupational and physical therapy are the only available recourse.

(05:11:45):

I want to thank the CCDS family for sharing with us the devastating impact of these disorders on their loved ones and their families. This impact is profound, robbing them of independence and engendering chronic isolation. It is clear from today that all CCDS are in dire need of therapies to manage symptoms, prevent further deterioration and improve quality of life. And now to close the meeting, back to Heidi in the studio.

Heidi Wallis (05:12:14):

Thank you for your thoughtful summary, Sangeetha. This has been an incredible day and helped us all better understand AGAT, GAMT and CTD, their impact on patients and their loved ones and the need for therapeutics of these disorders. Thank you to the FDA staff who tuned in today, and thank you to Will, Lou Allen from the FDA's patient focused drug development staff who guided us through this process over the many months of planning. Thanks also to Larry Bauer and James Valentine from Hyman, Phelps & McNamara, whose assistance in planning and moderating today's meeting has been invaluable. Thank you to the Dudley Digital Works media team for the production planning and all the behind the scenes work they have done today. And a big thanks to the ACD volunteers, staff, and board members who have given countless hours to the planning of today's meeting, including but not limited to Celeste Graham and Sung Chun.

(05:13:13):

And finally, a huge thanks goes to you, my fellow community of CCDS caregivers. Thank you for honestly sharing your lived experiences of CCDS today. This meeting could not have been as impactful or enlightening without each and every one of you. In the coming weeks, we'll compile all of the information from today, including polling data and comments into a voice of the patient report, which will be available on ACD's website. The form to submit comments for the report is open for another 30 days, so please consider submitting additional comments which will be added to the report.

(05:13:52):

A recording of today's program will be available and on demand immediately following this meeting. Today's meeting will have a lasting impact on the future of CCDS research and medical product development. So once again, to the entire community, thank you for making your voices heard today.

PART 10 OF 10 ENDS [05:15:15]