Externally Led Patient-Focused Drug Development Meeting for Cerebral Creatine Deficiency Syndromes (CCDS)
Voice of the Patient Report

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Cerebral Creatine Deficiency Syndromes (CCDS) Voice of the Patient Report

The Association for Creatine Deficiencies' (ACD) mission is to promote and fund medical research for treatments and cures, provide patient, family and public education, and advocate for early intervention through newborn screening for cerebral creatine deficiency syndromes (CCDS). This *Voice of the Patient* report was prepared on behalf of ACD as a summary of the input shared by families and caregivers living with CCDS during an Externally-Led Patient Focused Drug Development (EL-PFDD) meeting, conducted virtually on January 24, 2023.

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James Valentine, Esq. and Larry Bauer, RN, MA are employed by Hyman, Phelps & McNamara, P.C., a law firm that represents patient advocacy organizations and companies that are developing therapeutics and technologies to advance health.

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20 September 2023

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CCDS Key Insights

The following insights were captured at the January 24, 2023, Cerebral Creatine Deficiency Syndromes EL-PFDD meeting.

1. **For many, CCDS is diagnosed too late.** Diagnosis is traumatic and very little information is available about these disorders. Parents of children diagnosed with CTD expressed that at the time of their child's diagnosis, they were horrified to learn that there are no treatments available.
2. **Early diagnosis for GAMT and AGAT deficiencies makes a world of difference**. Supplementation with creatine monohydrate and other amino acids can prevent some, but not all symptoms and the long-term effects of these disorders is yet to be seen. Despite this, many individuals living with GAMT or AGAT deficiencies are not diagnosed and treated early enough to prevent neurological damage.
3. **Individuals living with CCDS experience many health concerns.** Speech impairment, developmental delay and intellectual disability are the most troublesome CCDS health concerns, followed by seizures and behavior issues, as well as many additional health concerns. Most symptoms are experienced by all subtypes, while some are characteristic of one subtype, for example, therapy-refractory epilepsy in GAMT deficiency. Symptoms tend to be more severe in individuals living with CTD; the longer individuals with GAMT or AGAT go without supplementation, the more severe their symptoms can be.
4. **CCDS has an enormous disease burden.** All activities of daily life are impacted, and families suffer. The inability to communicate effectively makes individuals living with CCDS vulnerable. Challenges with toileting/self-care, self-regulation and completing tasks compromise independence. Behavioral issues limit participation in society, and isolation is common for patients and their entire families.
5. **Parents have many worries for their loved ones' future.** They worry about who will care for their loved one after they pass, whether their loved one will ever live independently, if their symptoms will get worse and if new symptoms will appear. Parents also worry about their own physical and mental health.
6. **There are no FDA approved treatments for CCDS.** All individuals living with CCDS require a large number of different medications, supplements and medical consults, as parents will try anything possible to make a difference in the lives of their children. Most individuals living with CCDS require a great deal of supports including speech, occupational and physical therapy as well as school adaptations.
7. **Current CCDS treatment approaches and therapies are ineffective and require enormous effort and time commitments.** Individuals living with CTD have an urgent unmet need for effective treatments. Existing treatments for AGAT and GAMT deficiencies are not always effective and are enormously difficult to administer.
8. **CCDS families need treatments that work**. All individuals living with CCDS are in dire need of therapies to manage symptoms, prevent further deterioration and improve quality of life. CCDS is so devastating, even small improvements would make big differences for individuals and families. Improvements are needed for medication taste and administration. During the meeting, families identified other areas of improvement, especially medical knowledge of CCDS.

Introduction

The Association for Creatine Deficiencies (ACD) hosted the Cerebral Creatine Deficiency Syndromes (CCDS) Externally-Led Patient Focused Drug Development (EL-PFDD) meeting on January 24, 2023. This meeting was held to provide a patient, caregiver and family perspective of the symptoms and burdens associated with CCDS in daily life, as well as the massive unmet treatment needs experienced by patients and families who live with CCDS every day. The meeting was held virtually to enable as many community members to participate as possible and to allow many different voices to be heard.

CCDS are a group of inborn errors of creatine metabolism including creatine transporter deficiency (CTD), guanidinoacetate methyltransferase (GAMT) deficiency and L-arginine: glycine amidinotransferase (AGAT) deficiency. These are very rare diseases which are often diagnosed only after children have sustained neurological damage. While creatine and other supplements can help to mitigate some of the effects of GAMT and AGAT deficiencies, there is no treatment for CTD. Lifelong symptoms of CCDS often include delays in expressive speech and language, intellectual disabilities and developmental delay, seizures, autistic like behaviors, hyperactivity, projectile vomiting in infancy, failure to thrive, and movement disorders.

This EL-PFDD meeting was modeled after the work of the FDA's Patient Focused Drug Development (PFDD) initiative. PFDD is a systematic way of gathering patient perspectives on their condition and on available treatments. The CCDS EL-PFDD meeting objectives were to:

- Give patients and caregivers a platform to share with key stakeholders and the public what it means to live with or be a caregiver for someone who has one of the three CCDS, including symptoms, daily impact, and overall quality of life;
- Provoke discussions around existing treatments for AGAT and GAMT, and thoughts on future approaches to treatments for CTD;
- Publish and share a CCDS Voice of the Patient report following the meeting in fall 2023.

The information gathered at the meeting is presented in this *Voice of the Patient* report, a high-level summary of the perspectives generously shared by the families and caregivers of individuals living with CCDS, who participated in the January 24, 2023, EL-PFDD meeting. The report also includes selected comments submitted through the registration website and an online portal.

The information in this *Voice of the Patient* report may be used to guide therapeutic development and inform the FDA's benefit-risk evaluations when assessing therapies to address CCDS. The hope is that this information will catalyze better treatments and ultimately a cure for all those affected by CCDS.

ACD has provided this report to the FDA, government agencies, regulatory authorities, medical product developers, academics, and clinicians, and it is publicly available for the many stakeholders in the CCDS community.

Clinical Overview of Cerebral Creatine Deficiency Syndromes (CCDS)[1]

Cerebral creatine deficiency syndromes (CCDS) are a group of inborn errors of creatine metabolism. Creatine is an amino acid which is necessary to transport ATP in the cells of the body. Creatine is essential for brain function, so without it, brain function is impaired. Creatine can be synthesized within the liver and can also be ingested from the diet; many are familiar with creatine as a supplement taken to improve muscle strength.

The three different creatine deficiency syndromes include **L-arginine:glycine amidinotransferase (AGAT) deficiency**, **guanidinoacetate methyltransferase (GAMT) deficiency** and **creatine transporter deficiency (CTD)**.

Normally, creatine is synthesized in the liver from arginine, glycine and methionine in a two-step process involving the AGAT and GAMT enzymes. When these enzymes are impaired or deficient, creatine synthesis in the liver is inhibited.

- **AGAT deficiency** is the rarest of the three cerebral creatine deficiency syndromes, with less than 20 known patients reported worldwide to date. This autosomal recessive disorder results in a lack of creatine in the brain. Supplementation with creatine monohydrate can result in normal development, if started before 10 months of age.
- **GAMT deficiency** is also a rare, autosomal recessive disorder, with now more than 100 patients. The estimated prevalence of GAMT deficiency is 1 in 500,000-1,000,000. Similar to AGAT, GAMT deficiency results in a lack of creatine in the brain. However, GAMT deficiency results in the accumulation of guanidinoacetate (GAA), an intermediate in creatine synthesis, which is believed to cause neurotoxic effects. If untreated, GAMT deficiency results in a severe neurodevelopmental disorder with irreversible brain impairment. If patients are treated early and consistently, they may develop normally. Treatment cannot reverse damage from high GAA levels in late diagnoses and even with early diagnosis, GAA levels remain elevated with long-term impacts unknown.

Creatine is transported into cells via the creatine transporter, SLC6A8. In **creatine transporter deficiency (CTD),** the creatine transporter does not function properly and results in a lack of creatine uptake into the cell.

- **CTD** is the most frequent of the disorders, and is X-linked, which means that it was believed to primarily affect males. However, symptoms are now recognized in some females who carry the gene. More than 300 patients with CTD have been identified, and the disorder appears in about 1:200,000 individuals. While individuals living with GAMT and AGAT have

[1] Extracted from the presentations delivered at the EL-PFDD meeting on January 24, 2023, by Dr. Andreas Schulze, Hospital for Sick Children in Toronto, Canada, and Dr. Nicola Longo, University of Utah, Salt Lake City.

supplementation options available because of their ability to transport creatine, individuals living with CTD have none.

CCDS are primarily neurodevelopmental disorders. Symptoms vary between individuals and overlap between the three CCDS. When untreated, all three syndromes feature speech disturbances with little expressive speech and restricted comprehensive speech. All have global developmental delay and intellectual disability. All of the syndromes feature behavioral problems and autistic-like behaviors including impulsivity, hyperactivity, tantrums and aggression. Patients have muscular hypotonia and patients with GAMT have abnormal movements. All patients can have mild EEG or epilepsy changes, but unlike the other two syndromes, individuals living with GAMT deficiency can present with severe treatment-refractory epileptic syndrome. Other symptoms can include GI symptoms including failure to thrive or feeding intolerances.

Recently the Secretary of Health and Human Services approved the addition of GAMT to the recommended uniform screening panel (RUSP). Unfortunately, newborn screening for AGAT deficiency and CTD is still not available, and diagnosis must be based on genetic sequencing, MR spectroscopy or biochemical measurements, usually as a result of the onset of clinical symptoms.

For AGAT deficiency, therapy consists of providing high doses of creatine monohydrate three to six times per day. For GAMT deficiency, supplementation is similar to those with AGAT deficiency, with high doses of creatine monohydrate 3-6 times a day. In addition, individuals living with GAMT require additional supplementation to reduce the neurotoxic levels of GAA, including supplementation with high doses of ornithine (3-6 times a day) to reduce GAA synthesis, sodium benzoate supplementation to reduce glycine levels, and dietary restriction of arginine through a low-protein diet. For CTD, supplementation with creatine, arginine, and glycine is sometimes suggested, three times a day. It is not clear if this provides any clinical benefit except to a small subset of patients with some residual creatine transporter activity. SAME (S-adenosyl methionine) and betaine (3 doses a day) may also be recommended with unknown benefit if any.

EL-PFDD Meeting Summary

The Cerebral Creatine Deficiency Syndromes (CCDS) Externally-Led Patient Focused Drug Development (EL-PFDD) was held virtually on January 24, 2023. The meeting was an important opportunity for the Association for Creatine Deficiencies (ACD) to share patient and caregiver perspectives regarding the symptoms and daily impacts of CCDS, as well as thoughts on current and future approaches to therapies. The CCDS EL-PFDD meeting was structured around two key topics. The morning session was structured around *Living with CCDS - Symptoms and Daily Impact,* and the afternoon session focused on *Current & Future Approaches to Treatment for CCDS.* The meeting agenda is in **Appendix 1**.

The meeting was attended by 248 individuals, including one individual living with CTD, 124 parents and caregivers (4 AGAT, 26 GAMT, 98 CTD, 7 undeclared), 11 extended family members, 37 friends (4 AGAT, 4 GAMT, 16 CTD, 13 undeclared), 17 government representatives, 27 healthcare providers, seven industry representatives, 12 scientists, five non-profit representatives, and seven others.

EL-PFDD meeting attendees used online polling to indicate meeting demographics, shown in **Appendix 2**. The vast majority of EL-PFDD meeting attendees (95%) were caregivers for someone living with CCDS. Most meeting attendees were from the United States (72%), with representation from Central, Eastern, Pacific and Mountain time zones. The rest of the attendees were from Europe (12%), Canada (7%), Asia/Africa (7%) and Mexico/South America (2%).

Most individuals living with CCDS represented at the meeting were male (78%). The largest group of patients represented were 0-5 years of age (33%), followed by equal numbers of individuals aged 6 – 10 years and 11-18 years (27% each). Smaller percentages of patients were in the 19–30-year age range (11%) and the 31-50 age range (2%), with no one over the age of 50 represented. Individuals living with CTD were the largest group represented (79%), followed by individuals living with GAMT deficiency (19%) and AGAT (3%).

REGISTRY REFLECTION: Patient registry participants live in the United States (58%), Europe (21%), Canada (6%), Asia & Africa (6%), Australia (6%), and Mexico & Central/South America (5%). Similar to meeting attendees, most registry participants are male (80%). However, there is broader age representation among registry participants: 0-5 years of age (27%), 6-10 years (22%), 11-18 (33%), 19-30 (11%), 31-50 (6%), 50+ (0%). In total, registry participants with CTD represent the largest group (69%), followed by GAMT deficiency (29%) and AGAT (1%). All registry data was collected from ACD's CreatineInfo Patient Registry & Natural History Study for CCDS.

The meeting agenda is in **Appendix 2**, and the questions provided for meeting discussion are in **Appendix 3**, and meeting panelists and callers are listed in **Appendix 4.** The online polling results from Topics 1 and 2 are included in **Appendix 5**.

To include as many patient voices as possible, an online comment submission portal was open for four weeks after the meeting and comments were also collected through the registration portal. All submitted comments are included in a separate PDF document, with selected comments included in the body of this report. Additional reflections from the CreatineInfo Patient Registry and Natural History Study for (CCDS) are also included; a brief description of the registry can be found in **Appendix 6**.

The CCDS *Voice of the Patient* Report

This *Voice of the Patient* report is provided to all CCDS stakeholders including the US FDA, other government agencies, regulatory authorities, medical products developers, academics, clinicians, and any other interested individuals. The input received from the January 24, 2023, EL-PFDD meeting reflects a wide range of CCDS experiences, however not all symptoms and impacts may be captured in this report.

The final report, the accompanying document containing the submitted comments and a video of the meeting are available on the ACD website at https://creatineinfo.org/el-pfdd/. According to YouTube statistics, the meeting was streamed over 926 times as of September 9, 2023.

TOPIC 1: Living with CCDS - Symptoms and Daily Impacts

Patients, parents, and caregivers shared their perspectives and experiences of living with CCDS. Through moderated discussion and online polling, CCDS families described the CCDS-related health concerns that they or their loved ones experienced, the impacts of CCDS on activities of daily living, and their worries and fears for the future.

Key Insight: CCDS diagnosis is traumatic, especially as very little information is available about these disorders. Many parents shared stories about their children's initial symptoms and described long and convoluted diagnostic journeys which for some, took many years.

> *"Christina's [AGAT deficiency] 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."*- Jenny, mother of a 20-year-old daughter living with AGAT deficiency
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> *"Carly's quality of life was almost nonexistent. Life was a struggle… this was the worst time in our life. My daughter was dying before my eyes and I was helpless."* Even after diagnosis, much was unknown. *"No one understood GAMT back then. The treatments were not clear."* - Glenda, parent of a 23-year-old woman living with GAMT deficiency
>
> *"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."* - Brittany, parent of a three-year-old boy living with CTD

Key Insight: Parents were horrified to learn that there were no treatments available to mitigate CCDS symptoms, especially parents whose children were living with CTD.

> *"Even though we knew Crosby was behind developmentally and we were happy to finally have answers, it was still not easy news to [learn about his diagnosis]. 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."* - Kayla, mother of a four-year-old son with CTD
>
> *"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. We were told she was one of the first girls diagnosed in the world as primarily boys were tested and identified. The experts suspected that there were many undiagnosed children, and in the years since then, we've found that to be very true."* - Kimberly, mother of a 22-year-old daughter living with CTD

> *"In the fall of 2012, we… got the best/worst 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 were not only impacting Reid but our entire family."*- Whitnie, parent of a 12-year-old son living with CTD

Key Insight: Many children with GAMT deficiency were not diagnosed and treated early enough to prevent neurological damage. The recent approval of GAMT for newborn screening in the United States will likely change things for future generations.

> "*Daisy was one of the first GAMT cases diagnosed in the US when she was two years old. … GAMT has left Daisy severely intellectually delayed with severely limited communication.*" - Susie, mother of a 21-year-old daughter living with GAMT deficiency

> *"Her GAMT went untreated for nine years, has caused issues with her speech, severe learning delays, motor coordination, and epilepsy. Had this been on a newborn screen, we would have been able to start supplementation at birth and her life would have had a different path. Although she has made tremendous progress over the last year on supplements, she will need supports for the rest of her life."* - Marie, mother of a 10-year-old daughter living with GAMT deficiency

> *"He only started his creatine supplements at age 5. Had he started years before, the impact of his condition would not have been as severe."* - Jacob, father of a six-year-old son living with GAMT deficiency

Poll Questions 1 & 2

Individuals living with CCDS experience many health concerns. Speech delay or no speech and intellectual disability are the most troublesome CCDS health concerns, followed by seizures.

Parents and caregivers used online polling to select all of the health concerns that they or their loved one with CCDS ever had and to select the three most troublesome. Parents and caregivers each selected an average of 8.5 health concerns, an exceptionally high number, and they found it hard to choose which were the three most troublesome.

> *"It was hard to pick only three key symptoms that are bothering her life… depending on the days, one can be worse than the other one."* - Carole, mother of a 32-year-old woman with CTD

Poll results are presented in **Appendix 5, Q1 & Q2**, and are listed in the order of most troublesome below.

Speech delay or no speech.

Speech delay or no speech was selected as the most troublesome CCDS health concern and is experienced by almost all individuals living with CCDS. Parents described how speech and communication are further impaired by intellectual disabilities and developmental delays.

> *"He's never said mom or dad in his own voice, although he does use an assistive technology device, which is his voice."* - Jerry, parent of two children, aged 18 and 14, living with GAMT deficiency

> *"She does speak, but not at a four-year-old's level. She mostly imitates what you're saying."* - Christina, mother of four-year-old daughter and two-year-old son living with GAMT deficiency

> *"Our son wants very much to be able to speak, and he attempts to talk all day but probably 95% of his speech is not understandable. When he was around 3-4 years old, he had about a dozen words he said regularly that were quite clear, but he stopped saying many of those words around age 5*." - Erin, mother of a 7-year-old son living with CTD

> *"He's never had words. He's only babbled a little bit when he was a baby, then lost that. …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."*- Celine, mother of a 16-year-old boy living with CTD

Intellectual disability, developmental delay, and focus and attention challenges.

Intellectual disability and developmental delay were among the most troublesome CCDS-related health concerns and are experienced by 92% and 97% of people living with CCDS represented in the polls, respectively. **Focus and attention** challenges are experienced by 87% and are grouped here together as comments were so similar. Intellectual disability contributes to many other CCDS-related health concerns and is a challenging symptom to measure.

> *"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. … Carly was diagnosed with a developmental delay, cerebral palsy, autism, non-verbal and failure to thrive by five years old."* - Glenda, parent of a 23-year-old woman living with GAMT deficiency

> *"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."* - Rachel, mother of an 11-year-old boy living with CTD

> *"Similar to other CTD kids, he has global development delay that affects his day-to-day activities. His understanding is like a 2–3-year-old kid, with speech delay that doesn't allow him to communicate with others. … He cannot focus and concentrate on a topic*

and struggles in imitating which affects his learning abilities severely." - Ashkan, parent of an eight-year-old son living with CTD

Seizures.

Seizures were selected as one of the most troublesome CCDS-related health concerns and experienced by two-thirds of the individuals represented in the polls. Parents described how seizures sometimes led to a CCDS diagnosis, that seizures can be extreme and life threatening, and that seizures interfere with activities of daily life, learning, and language acquisition.

"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." - Jerry, parent of two children, aged 18 and 14, living with GAMT deficiency

"I would say the biggest impact is the seizures. In fact, seizures were what initially led to this diagnosis. 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 to 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. ... We're probably lucky if we get three weeks in between seizures, so it's fairly frequent." - Trey, father of a 19-year-old daughter and an 11-year-old son living with GAMT deficiency

Nathan's three sons experience extreme seizures. "*Simon currently has the most severe seizures, which can occur multiple times a day and last at least three minutes per episode. …Elijah has gone through periods of severe seizures in which a single episode can last more than 18 hours*." - Nathan, father of three sons living with CTD

Seizures have severe impacts including injuries and management requires advanced planning.

*"It's not necessarily the seizure activity that causes damage. **I**t'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."* - Trey, father of a 19-year-old daughter and an 11-year-old son living with GAMT deficiency

"*Thankfully, for Elijah and Ezra, seizure impact on daily life primarily involve planning considerations for the possibility that seizures will happen. ... Simon, on the other hand, has seen nearly every aspect of his life impacted by the treatment of seizures*." - Nathan, father of three sons living with CTD

Behavior issues (autistic-like behavior, self-injury, aggression, etc.).

Many parents described behavior issues ranging from ADHD, impulsivity, tantrums, elopement, screaming in public, self-harm, property destruction and even violence towards others, necessitating police involvement and even restraints. Intellectual disability and an inability to

clearly communicate can contribute to frustration and aggression. Behavior issues can interfere with relationships inside the family and can result in social isolation of the entire family.

> *"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."* - Whitnie, parent of a 12-year-old son living with CTD

> "*The behavior, of course, is linked to the intellectual disability. …She pulls her hair, she run away in the street, she can break a window. She's quite unpredictable when she's bad. … 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.*" - Carole, mother of a 32-year-old woman with CTD

> *"His self injurious behaviors, aggression and screaming take a toll, but then also going limp, eloping and his extreme impulsivity. … 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."* - Celeste, mother of an 11-year-old son living with CTD

> *"Extreme behavior problems have been the constant symptom of this horrible disease and have affected every aspect of Daisy's and our lives. … 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 property. … 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."* - Susie, mother of a 21-year-old daughter living with GAMT deficiency

Other CCDS-related health concerns.

Other CCDS-related health concerns selected in the polls include **failure to thrive**, **gross motor challenges (walking, running, climbing)**, **gastrointestinal (GI) problems (constipation, vomiting, reflux)**, **fine motor challenges (pencil grasping, using scissors, zipping)** and **movement disorders (involuntary movements and tremors)**. Many parents described challenges in particular with eating, slow feeding, reflux and vomiting which led to malnutrition, extreme weight loss and eventual G-tube installation.

> *"He struggles with weight issues I am always emotional when we take his clothes off, he's very skinny."* - Irene, mother of a three-year-old son living with CTD

> *"Feeding struggles and projectile vomiting became a way of life for us and a constant source of anxiety. … Reid was thin and battled to make up ground on the growth chart*."
> - Whitnie, parent of a 12-year-old son living with CTD

During the meeting and in the submitted comments, parents mentioned a wide range of other health concerns that were not included as poll options. These illustrate how variable CCDS-related health concerns can be. **Prolonged QT syndrome and other cardiac abnormalities**, **hypoglycemia**, **dystonia** (muscle spasms and contractions), **hypotonia** (low muscle tone), **breath-holding**, **severe sleep issues**, **frequent infections**, **sensory issues including very high pain tolerance, torticollis** (head tilted sideways), **visual issues, pulmonary issues, auditory processing disorders, incontinence, anxiety**, **specific antibody deficiency,** and **asthma**.

REGISTRY REFLECTION: CreatineInfo Registry participants report a wide range of symptoms related to CCDS. The top reported symptoms are global developmental delay (83%) and speech delay (76%), followed by seizures (52%) and autism features (50%). Other symptoms reported in the registry include hypotonia, attention deficits, low weight, food aversion (e.g., eating difficulties), behavior problems, gastrointestinal problems (e.g., reflux, bloating), heightened pain tolerance, failure to thrive, constipation, low/high activity levels, movement disorders (e.g., dystonia or dyskinesia), diarrhea, cardiac conditions (e.g., prolonged QT, abnormal heart rhythms), dysmorphic facial features, tremors, breath-holding, learning difficulties, respiratory problems, sleep disturbances, sensory processing disorder, and fine/gross motor delays.

Poll Question 3

CCDS has an enormous disease burden, as all activities of daily life are impacted.

Parents and caregivers used online polling to indicate the top three specific activities of daily life that their loved one with CCDS struggles with. Poll results are in **Appendix 5, Q3**. The most impacted activity was **communicating effectively**. The next three poll responses were tied: **toileting/self-care behaviors**; **self regulation, impulse control, and executive function**; **completing daily tasks independently**. Many parents spoke about how hard life was for their children. For AGAT & GAMT patients without early diagnosis and supplements, and for all CTD patients, nearly all activities of daily living are impacted, and patients are unable to live independently.

Key Insight: CCDS has a profound impact on families. The impact on families and siblings was emphasized throughout the meeting. The enormous caregiving burden of CCDS leaves parents with little independence or time for anything or anyone else including the siblings of affected children. Families are unable to travel and can be socially isolated due to their child's behavior.

> *"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." - Susie, mother of a 21-year-old daughter living with GAMT deficiency

"Xavier's CTD has had tremendous impacts on our family life. He requires near constant supervision to ensure his safety and emotional well-being. My husband and I always feel stretched too thin and constantly worry that our older, neurotypical son is not getting the attention he needs. Finding babysitters who are willing and competent to care for Xavier is extremely difficult, and we do not have family members who are able to provide that support. For this reason, my husband and I have not had a single night away from Xavier for the past 10 years, and we went over three years without even having an evening together away from home. As you can imagine, this takes its toll on our mental health and relationship. We avoid settings that are too crowded or where we cannot closely supervise his safety, which limits our ability to form friendships with others." - Barbara, mother of a 12-year-old son living with CTD

"Public outings and finding respite care became nearly impossible. We lived within our walls and we trudged on… 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." - Whitnie, parent of a 12-year-old son living with CTD

Communicating effectively is the activity most severely impacted by CCDS.

Communicating effectively can be impacted by intellectual disabilities as well as speech challenges, and communication frustrations can lead to behavioral issues. Individuals who are unable to communicate effectively are vulnerable. A specific concern raised throughout the meeting concerned patients' inability to communicate if they were in pain.

"*It's hard for him to communicate his wants and needs. …I feel like sometimes when he gets frustrated or irritated or even when he's in pain he's not able to pinpoint those. And so sometimes we see that come out in behaviors when he is not able to communicate effectively with us*." - Rachel, mother of an 11-year-old boy living with CTD

"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." - Celine, mother of a 16-year-old boy living with CTD

Horrifyingly, Regina's grandson walked on an undiagnosed hip fracture for almost a year. *"He was unable to tell us that he was feeling uncomfortable or whether or not he could even feel that pain. … 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."* - Regina, caregiver of a 28-year-old daughter and a nine-year-old grandson, both living with CTD

Some parents described how hard they worked to communicate with their children, which touched on another CCDS impact selected in the polls, **following complex instructions**.

> Trey described how he communicates with his daughter. *"Slowly and positively … 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 be able to really figure that out."* - Trey, father of a 19-year-old daughter and an 11-year-old son living with GAMT deficiency

Toileting/self-care behaviors and completing daily tasks independently are impacted, compromising independent living.

CCDS impacts all aspects of personal care, from personal hygiene to making meals. Toilet training children with CCDS is a long and challenging task and some remain incontinent. Parents described how hard it was to find caregivers to assist them, increasing dependence on the parents. Some children are so severely affected that they require residential or respite care.

> Despite being treated from 10 months old, Kim's son still has problems with self-care. "*Having [no] 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*." - Kim, mother of a 17-year-old son and a 13-year-old daughter living with GAMT deficiency
>
> *"They are 12 and I am still tying their shoes, brushing their teeth, helping them to figure out how to move their arms in shower to wash on their own. I am still helping them with toileting needs. They want to be independent and be like their peers at school."* - Jenny, mother of identical 12-year-old twin boys living with GAMT deficiency
>
> *"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."* - Whitnie, parent of a 12-year-old son living with CTD
>
> *"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 be a girl with CTD*." - Kimberly, mother of a 22-year-old daughter living with CTD
>
> *"Given the lack of any effective treatment for CTD, we expect that Xavier will need care with all aspects of daily life as he progresses toward adulthood."* - Barbara, mother of a 12-year-old son living with CTD

Self-regulation, impulse control, and/or executive function as well as regulating emotions limits participating in regular life.

Parents described how a lack of **self-regulation, impulse control and/or emotional control** and **regulating emotions appropriately** can result in tantrums and screaming in public or inappropriate behavior such as hugging and kissing strangers. This severely limits participation

in society, time spent in public, and even travel. For some, safety is a concern as some individuals living with CCDS will wander off.

> *"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."* - Susie, mother of a 21-year-old daughter living with GAMT deficiency

> *"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. 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."* - Kimberly, mother of a 22-year-old daughter living with CTD

> *"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. … 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*." - Christina, mother of a 13-year-old daughter living with CTD

Educational impacts: Learning at the same rate as their peers and having adequate health to attend school or work.

During the meeting many described how challenging it was for their child to **learn at the same pace as their peers.** Seizures, behavior issues, and other challenges can **make it impossible to participate with their peers in a general education classroom without assistance**. Most require some adaptation and accommodation, and possibly alternative classroom settings. Some described moving the entire family so that their child could attend a school that better addressed their educational needs.

> *"For my son, there's a very narrow window of equilibrium where he can focus … so the stars have to align so he can acquire any skill and it requires a tremendous amount of effort."* - Laura, mother of an eight-year-old son with CTD

> *"Around kindergarten, … we tried to 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."* - Trey, father of a 19-year-old daughter and an 11-year-old son living with GAMT deficiency

> "*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."* James has moved his son from one school to the next to find the right education setting. "*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."* - James, father of a six-year-old boy living with CTD

Parents and caregivers also shared the impacts of CCDS on their employment and family finances. Often, one parent quits work to care for their loved one or they are only able to work when their child is at school.

> "*CTD severely impacts the lives of every family member of an individual living with the condition. The amount of care required caused us to drop from a two-income family to a one income family*." - Jolene, mother of a child living with CTD

> *"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."* - Beth, mother of an 18-year-old son and a 14-year-old daughter living with GAMT deficiency

> *"We become economic burdens on society as we are forced to remove ourselves from our careers to be caretakers instead. We become reliant upon social programs, rather than contributing to the community. We cannot engage in community, and this is detrimental to the mental health of all."* - Regina, caregiver of a 28-year-old daughter and a nine-year-old grandson, both living with CTD

Engaging in social interactions are limited, leading to isolation.

Based on the large number of comments made at the meeting, **engaging in social interactions** is severely impacted by CCDS. Many individuals living with CCDS will never have friends or romantic partners. Intellectual disability, developmental delay, speech and behavior challenges all play a role in social isolation. Individuals living with CCDS are socially isolated, as are their families.

> *"It's a struggle as a parent to watch them get left behind in academics, sports, and other typical pre-teen experiences. The friendships they are supposed to have at this age, are non-existent. I am lucky they have each other, but I know they could have had so much more if their diagnosis was caught at birth."* - Jenny, mother of identical 12-year-old twin boys living with GAMT deficiency

> *"Her social life consists of her family and relatives and maybe a few friends at her school. She wants to be social, but when you can't really communicate in a normal way, that*

becomes a challenge. You can tell she has a desire to be with other kids, and she's happier with other people. … That interaction is obviously limited because of her ability to both process and produce good speech." - Trey, father of a 19-year-old daughter and an 11-year-old son living with GAMT deficiency

"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." - Kimberly, mother of a 22-year-old daughter living with CTD

Unable to socialize, play or interact with others. "*Levi has a desperate want to interact with others. … He loves to hug his classmates; however he doesn't know his own strength. 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*." - Celeste, mother of an 11-year-old son living with CTD

Even those with GAMT and AGAT who were diagnosed early enough to have improved social skills, reported experiencing social impacts as a result of their rigorous supplement regimens.

"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 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 of a day-long Nutcracker rehearsals in order to gulp down my medication, so the other dancers would not notice." - Christina, 20-year-old woman living with AGAT deficiency

"The challenges she faces now are mostly social. … 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." - Jerry, parent of two children, aged 18 and 14, living with GAMT deficiency

Other CCDS impacts.

Another important CCDS impact not captured in the polls but mentioned during the meeting was **challenges in obtaining routine medical care.**

"The combination of autistic-like sensitivity to stimuli and low receptive language makes it difficult for him to access routine medical care. For example, dental interventions must

be done under general anesthesia." - Barbara, mother of a 12-year-old son living with CTD

Poll Question 4

Parents have many worries for the future. They worry about who will care for their loved ones after they pass and whether they will be able to live independently.

Parents and caregivers used online polling to select their top three worries about their loved one's condition in the future. Poll results are in **Appendix 5, Q4**, and are listed in the priority order, along with patient and caregiver quotes.

The top worry is for how their loved ones will be cared for after their caregivers pass.

Many parents with dependent children worry if they will **be cared for after they pass**. They worry about **safety** and they expressed concerns about exploitation and whether assisted living is appropriate for such vulnerable individuals. Some parents hoped that their child's siblings would assist them later in life.

"*Nobody could care or love her like me. …I will be taking care of Daisy the rest of her life. She is my life."*- Susie, mother of a 21-year-old daughter living with GAMT deficiency

"Who will take care of Benny when we're gone? … Nobody wants to leave a completely vulnerable child in their care in the hands of somebody else." - Beth, mother of an 18-year-old son and a 14-year-old daughter living with GAMT deficiency

"*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*." - Kimberly, mother of a 22-year-old daughter living with CTD

"I worry about their future and mine. … I'm not dreaming about their future for college, marriage and grandchildren. I'm worried that they won't be safe and loved and cared for properly when I'm gone." - Jenny, mother of identical 12-year-old twin boys living with GAMT deficiency

Worries about living independently.

Many parents worry if their children would **be able to live independently in the future**. Some worry about whether their children will be able to successfully administer their own medications without assistance.

"We recently went through a period within the past year where we did not supervise him as closely and trusted that he would [take his medication] on his own. … One day we happened to catch him throwing out part of his supplement mixture, … disposing as

much as he could just because he hated taking it so badly. … *It was a reminder that we don't know how self-sufficient Max will become as he gets older.*" – Leif, father of a 13-year-old son living with GAMT deficiency

"*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*. … *We lament what could have been for Benny and worry about his future without us*." – Jerry, parent of two children, aged 18 and 14, living with GAMT deficiency

"*My child's projected trajectory 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*." – Ted, caregiver for a son living with CTD

Worries that their loved ones' symptoms will get worse or that new symptoms will appear.

Parents worry about the many unknowns of these disorders, including the potential emergence of new symptoms.

"We are worried about the long-term effects of increased GAA levels." - Carien, parent of a two-year-old son living with GAMT deficiency

"*How will GAMT affect him going through puberty? Will he grow at the same rate? Will GAMT affect his thought process 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. Will GAMT affect his emotional state? Will he be able to continue to work towards self-sufficiency or will he regress?"* - Leif, father of a 13-year-old son living with GAMT deficiency

"*We don't have much information of how CTD evolves when you get older. And so maybe, there will be more symptoms or unknown symptoms or other things evolving the wrong way. So that's one of the key concerns*." - Carole, mother of a 32-year-old woman with CTD

"*We also have a constant concern that his health conditions get worse given that some CTD kids started suffering different health issues when they get older such as heart and kidney problems."* - Ashkan, parent of an eight-year-old son living with CTD

Worries that their loved one will be unable to communicate needs.

Parent worry about their loved one **not being able to communicate needs**, especially their pain and their emotions.

> "*It's hard for him to communicate his wants and needs. … 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*." - Rachel, mother of an 11-year-old boy living 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."* - Kimberly, mother of a 22-year-old daughter living with CTD

> "*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*." - Kayla, mother of a four-year-old son with CTD

Worries about the impact of CCDS on the caregiver's physical/mental health.

Many caregivers expressed worries about their own physical and mental health, which speaks to the heavy burden of this disease. One even described how their family developed "armor" and a "thick skin" to deal with their loved one's disease. Others expressed shame and guilt.

> *"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. … The biggest turning point in our lives from enduring the constant struggles of this disease was in 2018 when I had a mental breakdown. 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.* - Susie, mother of a 21-year-old daughter living with GAMT deficiency

> Carole experienced judgement about her parenting and shame before her daughter was finally diagnosed with CTD. *"When she was 18 months, she was a bit different from the others. … They thought it was maybe something related to the mom, to myself actually, how I raised her and maybe there was some psychological problem. …We had a sense of guilt of what we have done wrong or not. When she turned 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."* - Carole, mother of a 32-year-old woman with CTD

Worries about developing medication intolerances /side effects.

Patients and caregivers worried about whether their treatments will be still effective in the future and whether intolerances or side effects will develop.

> "*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?"* - Christina, 20-year-old woman living with AGAT deficiency

> *"While Xavier has had few seizures, the ones he has had required hospitalization with sedation and artificial respiration. We are fortunate that he has responded well to anti-seizure medications but are worried that someday his medications will become less effective."* - Barbara, mother of a 12-year-old son living with CTD

Other worries.

Parents used online polling to select other worries including worries about the **impacts of social relationships,** worries about the **impacts on job or school** and **other** worries. Parents expressed other worries not included in the polls, including **worries that their child would hurt someone**, that **the lack of healthcare providers with CCDS knowledge would limit appropriate therapy being offered**, worries about **whether to have additional children** and **whether those children would have CCDS.**

Topic 2: Current & Future Approaches to CCDS Treatment

Through online polling and moderated discussion, patients, parents, and caregivers described all the different medical treatments that they use to manage CCDS-related symptoms, as well as other therapies and supports. They described the most significant drawbacks associated with each approach and articulated their hopes for future ideal CCDS treatments.

Key Insight: There are no FDA approved treatments for CCDS. This highlights an enormous unmet need in individuals living with CTD, who have no treatments. Existing treatments for AGAT and GAMT deficiencies are not always effective and are enormously difficult to administer.

Poll Question 5

Creatine monohydrate is the top medical treatment used to treat the symptoms of CCDS, followed by anti-seizure medications and supplements.

Parents and caregivers used online polls to select all the medications and medical treatments that the individual living with CCDS used (currently or previously) to treat CCDS symptoms, which really highlights the differences between the different CCDS subtypes. Poll results are presented in **Appendix 5, Q5**, and listed in descending order below. Each respondent selected an average of 4.7 different medications, and none indicated that they have not used medications or medical treatments. This speaks to the enormous burden of these disorders.

Creatine monohydrate.

Creatine monohydrate, a treatment for both GAMT and AGAT deficiencies, and sometimes tried by CTD patients with varying or no improvements, was the top CCDS treatment selected in the polls. Those with AGAT and GAMT who were diagnosed and treated early enough showed remarkable improvements.

> Christina was diagnosed at 16 months. *"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."* - Jenny, mother of a 20-year-old daughter living with AGAT deficiency
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> *"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."'* - Amy, mother of a one-year-old daughter living with GAMT deficiency
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> *"My child lives a pretty normal life since he was screened at birth and started treatment right away. He does not show any symptoms of GAMT. We are so, so thankful for the newborn screening."* – Becky, mother of a son living with GAMT deficiency

Parents compared the outcomes of their children who received early diagnosis and treatment with the outcomes of older siblings who started treatment later in their lives.

> *"Samantha was diagnosed at five and has lifelong developmental delays and speech challenges and seizures. And Louis was diagnosed at birth and does not have those effects, but still needs to obviously take supplements."* - Trey, father of a 19-year-old daughter and an 11-year-old son living with GAMT deficiency
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> *"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. … We love spending time with him, but we are sad for the opportunities that he missed out on that Celia does have. … She is in a regular classroom in eighth grade. She gets straight As, 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*." - Beth, mother of an 18-year-old son and a 14-year-old daughter living with GAMT

Creatine monohydrate has many drawbacks.

- Creatine needs to be administered early in development to make a difference for individuals living with AGAT and GAMT deficiency. Supplements cannot reverse neurological damage, but there are benefits that sometimes include seizure control and better behaviors.

> "*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." - Jacob, father of a six-year-old son living with GAMT deficiency

Benny started taking supplements at the age of six. "*The biggest advantage of treatment for Benny was that he was able to come off seizure medications completely and went years without a seizure."* - Jerry, parent of two children, aged 18 and 14, living with GAMT deficiency

- Creatine monohydrate treatment does not alleviate the burden of disease for those living with CTD. Yet, based on the high ranking of creatine monohydrate in the poll results and comments, many living with CTD take this treatment because there is simply nothing else.

"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. There's no evidence that it does anything." - Dan, father of a seven-year-old son living with CTD

"*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. Also, it smelled and tasted like a garbage bin the morning after a fish fry*." - Zigmas, father of a 13-year-old daughter living with CTD

- Administration of creatine monohydrate and other required supplements is extremely challenging due to the large amounts of horrible tasting supplements that must be consumed multiple times a day, especially for those who have an intellectual disability and don't understand the importance of taking their medications.

"*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. … 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*." - Leif, father of a 13-year-old son living with GAMT deficiency

"*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."* - Jenny, mother of identical 12-year-old twin boys living with GAMT deficiency

- The optimal amount of creatine monohydrate to treat these rare disorders is unknown.

> *"It has also been unclear how much creatine monohydrate I needed to take. … 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."* - Christina, 20-year-old woman living with AGAT deficiency

Anti-seizure medications.

Anti-seizure medications were the second most selected medication in the online polls. Some CCDS patients try every anti-seizure medication available. A few types of anti-seizure medications mentioned during the meeting include levetiracetam (Keppra), oxcarbazepine (Trileptal), pentobarbital, cannabis derivatives including Epidiolex or CBD oil, and emergency rescue medications. Some report that seizure medications can help.

> By the age of three, Jerry's son, "*was treated with anti-epileptics or cocktails of them with mild positive results. Void of 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."* - Jerry, parent of two children, aged 18 and 14, living with GAMT deficiency
>
> *"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.* – Nathan, father of three sons living with CTD

Seizure medications also have many downsides.

- Some individuals living with GAMT deficiency are resistant to seizure medications.

> *"My daughter suffers from seizures that are not controlled by the supplement and diet approach to GAMT. They are not controlled by seizure medicines. … She has fallen and been injured many times from her seizures. We are frequenting the emergency room and I don't see an end in sight."* - Heidi, mother of 19-year-old daughter and an 11-year-old son living with GAMT deficiency
>
> *"He takes medication for absence seizures twice a day, and we've already had to increase it twice. Although it is working, the seizures are not completely gone. But before he started treatment, he was having seven seizures an hour."* - Christina, mother of four-year-old daughter and two-year-old son living with GAMT deficiency

Seizure medications become ineffective as the patient becomes tolerant, leading to an increase in medication levels.

"*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. …Then with medication adjustments, it would get better for a while before the medications would not be as effective or would have to change [because of] side effects*."- Glenda, parent of a 23-year-old woman living with GAMT

"*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. …Simon has seen his medications slowly increase over the past year as he appears to build up a tolerance to his existing regimen*. …*Further, given his high resistance to or complete ineffectiveness of most emergency anticonvulsants, unique protocols have been put into place to respond to any seizures that occur."* - Nathan, father of three sons living with CTD

- Seizure medications have side effects including drowsiness, dizziness, and disorientation.

"The massive doses of [seizure] 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." - Nathan, father of three sons living with CTD

Supplements (multivitamins, others) as well as glycine and arginine for CTD.

The third most selected medication or medical treatment for individuals with CCDS in the polls was supplements including multivitamins. Some of the supplements mentioned at the meeting included SAME (S-adenosyl methionine), leucovorin, B6, taurine, L-ornithine, and betaine. In the polls, the fourth and fifth selected poll responses were arginine and glycine. Supplementation with creatine, arginine and glycine is sometimes suggested for individuals living with CTD.

"*Sam and Louis 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*." – Heidi, mother of 19-year-old daughter and an 11-year-old son living with GAMT deficiency

"*I use a lot of supplements so far as B6, taurine, just the different amino acids that calm him and they have worked. … He is at a high dosage right now and I am seeing some benefit from that*." - Beth, mother of 28-year-old son living with GAMT deficiency

"*Although there is no treatment for CTD, we still give our son many supplements, in hopes that perhaps they will help give him even a 1% boost in cognitive abilities. Currently we mix creatine gluconate, arginine, glycine, betaine, and SAMe with orange*

> *juice multiple times per day, and he also takes leucovorin once a day, all under the guidance of his metabolic specialist*." - Erin, mother of a 7-year-old son living with CTD

Supplement drawbacks include the lack of proven efficacy for some, terrible taste, and patients sometimes throw them up.

Behavior medications.

Over a third of poll respondents reported using **behavior medications** including medications for ADHD or to treat anxiety.

> *"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. …His developmental pediatrician 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*." - Celeste, mother of an 11-year-old son living with CTD

> *"Reid's behaviors and seizure management were constant and ranged from ABA to supplements, to antipsychotics."* - Whitnie, parent of a 12-year-old son living with CTD

Behavior medication drawbacks: they don't always work, and sometimes dose escalation is required.

> Glenda's daughter experienced combative and aggressive behaviors after her seizures started. "*We tried different medications for mood, but they made it worse. She was always struggling."* - Glenda, parent of a 23-year-old woman living with GAMT

Other medications and medical treatments.

Other medications and treatments selected in the polls included **anti-nausea medicines or laxatives**, **sleep medication**, and **pain medications (NSAIDs, prescriptions)**. A point made throughout the EL-PFDD meeting was that individuals living with CCDS require large amounts of medications, supplements, therapies, and medical consults.

Other medications and medical treatments not included in the polls but captured during the meeting include **reflux/GERD (gastroesophageal reflux disease) medications, appetite boosters,** and **surgeries including g-tube placement and brain surgery**.

Poll Question 6

Speech therapy, occupational therapy, and physical therapy are required by almost all individuals living with CCDS.

Parents and caregivers used online polling to select all the tools and approaches - besides medications and medical treatments - that the person living with CCDS used to help manage symptoms. Each respondent selected an average of 5 different approaches, and again, not one of the poll respondents replied that they are not using any approaches to manage symptoms. Poll results are presented in **Appendix 5, Q6**, and are listed in descending order of preference.

Speech, occupational, and physical therapy.

More than 80% of individuals living with CCDS represented in the poll results receive all three therapies, many initiating therapies even before a formal diagnosis was obtained. These therapies can also include ABA (applied behavioral analysis) therapy.

> *"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. …Luca receives occupational therapy, physical therapy, and developmental intervention in the home. He is completely non-verbal*." - Christina, mother of four-year-old daughter and two-year-old son living with GAMT deficiency

> "*He's pretty much lived his entire life from four months of age through nine [years] in therapies. … He's made great progress with it. I think that the key there is that it was a very early intervention. Although 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."* - Regina, caregiver of a 28-year-old daughter and a nine-year-old grandson, both living with CTD

Speech, occupational, and physical therapy drawbacks: All of these therapies demand a great deal of time and can interfere with other educational and social activities. For some, a great deal of travel is involved.

> Regina's grandson's private and school-based therapies interrupt his academic studies. "*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 himself 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."* - Regina, caregiver of a 28-year-old daughter and a nine-year-old grandson, both living with CTD

> *"Living in a rural area makes it really hard to get services. Finding time to make it to the therapy appointments is really tough when we have to travel and we both work full time. …This past summer, we spent two to 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.*" - Kayla, mother of a four-year-old son with CTD

School adaptations.

Many individuals living with CCDS require school adaptations and accommodations. Some are segregated in life skills programs while many receive school-based therapies as part of an individualized education program, (IEP). Some work with special education teachers to improve behavior, self-regulation, speech, and the ability to focus and understand. Some attend alternative education programs.

> *"At the age of 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."* - Christina, mother of four-year-old daughter and two-year-old son living with GAMT deficiency

> *"Our daughter goes to a typical school with assistance offered to her through her IEP. … She receives behavioral intervention, speech therapy, and works with a number of special education teachers inside her class as well as in special meeting rooms when she's pulled out of class."* - Zigmas, father of a 13-year-old daughter living with CTD

School adaptation drawbacks: Some parents were not certain if these made a difference.

> *"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."* - Zigmas, father of a 13-year-old daughter living with CTD

Other therapy approaches or strategies (horse, music, etc.).

Over half of poll respondents indicated that they use **other therapy approaches**, including hippotherapy (horse therapy). They also mentioned using **different strategies** to manage CCDS, including avoiding triggers and de-escalation.

> "*He's 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.*" - Celeste, mother of an 11-year-old son living with CTD

> "*Intensive ABA interventions helped us manage his most challenging behaviors and our family has become very skilled at responding to his behaviors and helping him de-escalate*." - Barbara, mother of a 12-year-old son living with CTD
>
> Some families work hard to avoid, *"triggers like loud noises that would lead to a physical attack on whoever was in arm's reach."* - Whitnie, parent of a 12-year-old son living with CTD

Dietary changes (such as low protein or gluten-free, etc.).

Parents described a wide range of dietary adaptations depending on the disease subtype. GAMT patients typically follow a low protein diet. Occasionally, other diets are tried in order to address CCDS symptoms.

> "*We 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*." - Glenda, parent of a 23-year-old woman living with GAMT deficiency
>
> "*We treat 4 times a day with dosages of creatine, ornithine and sodium benzoate and follow a restricted protein diet under supervision of a dietitian at the children's hospital*."- Amy, mother of a one-year-old daughter living with GAMT deficiency
>
> *"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 carbs 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."* - Zigmas, father of a 13-year-old daughter living with CTD

Diet drawbacks: These extreme diets are impossibly hard to adhere to, patients often have a hard time finding enough to eat and can suffer nutritional deficits. Some parents question whether there is enough scientific evidence to support these approaches.

> *"Right now, we're limiting the amount of protein these kids can eat. And that also has an impact. So if you take Louis … 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. He's not a big kid, and we're concerned about that."* - Trey, father of a 19-year-old daughter and an 11-year-old son living with GAMT deficiency
>
> "*Our healthcare professionals lack data and research to provide a great action plan for treatment using a low protein diet. They would like our daughter on 25 grams of protein per day. This is another hurdle. Our daughter is hungry and our own research doesn't*

align with the guidance of our healthcare team." - Stephanie, mother of a daughter living with GAMT

Other treatment approaches selected in the polls.

Parents selected a number of other tools, therapies and approaches that they used to manage the CCDS symptoms. These include **leg braces/orthotic devices**, **counseling or psychotherapy** including behavioral therapy, **chiropractic care**, **wheelchairs**, and **acupuncture**.

Poll Questions 7 & 8

Current CCDS treatment approaches are not very effective at treating target symptoms and require enormous amounts of effort and time.

Parents and caregivers used online polling to indicate how well their loved one's current treatment regimen treats the most significant symptoms of CCDS and to select the three biggest drawbacks. Poll results between **Q7** and **Q8** were consistent and are in **Appendix 5**.

Treatments are not very effective at treating target symptoms or only treat some, not all of the symptoms.

There still are no FDA approved treatments for any of the CCDS conditions and no disease modifying therapies. Top drawbacks included **not very effective at treating target symptoms** and **only treats some, not all the symptoms**, consistent with results of poll question 7, where 78% of poll respondents selected that their treatment regimen only helped **somewha**t, **very little**, or **not at all** to treat the most significant symptoms of CCDS.

"We tried supplements for my son who has CTD and really didn't see any impact from using them." - Jolene, mother of a child living with CTD

"He started therapies OT, and PT as early as six months old, but we have not seen any significant improvement. At three years old he cannot sit, stand or walk and he is mostly floppy or stiff." - Irene, mother of a three-year-old son living with CTD

Some described how the medications **only treat some, not all symptoms**.

"No matter what meds we try they don't truly help CTD. Yes, [they help] manage seizures and sometimes behaviours but that's all." - Vicky, mother of a 20-year-old son living with CTD

"It's tough to answer this poll question. His seizures are managed right now, but his speech and other skills are not." - Kayla, caregiver for an individual living with CTD

Parents indicated how hard it is to evaluate whether treatments are working at all.

"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 his therapies or the supplements that we do use are doing anything."* - Dan, father of a seven-year-old son living with CTD

In poll **Q7**, ten percent of poll respondents indicated that treatment helps, **to a great extent**. This was likely selected by AGAT and GAMT families whose loved ones received early treatment, however, some AGAT/GAMT families experienced treatment deficits. Some parents described having to accept that the improvements that their children would experience are limited.

> "*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*." - Kim, mother of a 17-year-old son and a 13-year-old daughter living with GAMT deficiency

> *"When they're very young, you don't want to accept [the lack of treatment efficacy], 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*." - Trey, father of a 19-year-old daughter and an 11-year-old son living with GAMT deficiency

Requires too much effort and/or time commitment.

The second most selected drawback is that treatment **requires too much effort and time commitment**. Throughout the EL-PFDD meeting, patients and families described the enormous amount of time and effort required for therapies and to take supplements.

During the meeting they also described the amount of time and effort it takes to measure and mix the supplement powders accurately. Some described how their kitchens resembled laboratories and some even tried compounding powder into pills. Parents also described the incredible amount of time and effort it takes to administer these supplements.

> *"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*." - Randy, father of a five-year-old child living with CTD

> "*Aside from not having any viable treatments for CTD, the therapies are extremely time consuming- and life altering for all involved*." - Sidney, parent of a child living with CTD

> "*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 continued for years with a lot of times not being able to give her the*

> *prescribed dosage, resulting in what I think caused damage to her brain*." - Susie, mother of a 21-year-old daughter living with GAMT deficiency

Administration is challenging and time consuming even for children who have G-tubes.

> "*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 has to get her next dose. In dance, the restrictive clothing irritates the port site and she asks for accommodations during costuming to make sure her port is covered or not obvious."*- Jerry, parent of two children, aged 18 and 14, living with GAMT deficiency

Monitoring and testing activities and time spent in hospital all take a toll.

> "*Between tests and surgeries and visits to the doctor, the time Simon has spent in the hospital can be measured in months."* - Nathan, father of three sons living with CTD

> *"She's getting blood work drawn almost every month. …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."* - Christina, mother of four-year-old daughter and two-year-old son living with GAMT deficiency

High cost or copay, not covered by insurance.

As supplements for CCDS are not officially indicated or approved for these conditions, obtaining insurance coverage can be difficult. Even when the medications are covered by insurance, it takes a great deal of work to apply for the coverage and fill in all the forms. Some parents even described challenges obtaining reimbursement or financial support for essential therapies.

> *"We do have pretty good medical insurance. But it's almost a full-time job for someone to manage getting [coverage]. 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."* - Dan, father of a seven-year-old son living with CTD

Long-term safety concerns and medication side effects.

Parents expressed concerns about **long term safety** from the dietary restrictions, supplements, and medications.

> "*The current treatment also has unknown potential dangers. There is the risk of kidney damage from microcrystalization of creatine in the renal tubules, for example. The effect of dietary restrictions on growth and development. The potential effect of high-dose ornithine on growth hormone production. We have no idea how much of each treatment is needed for a newborn or the dangers to a newborn. But these are treatments given*

> *because they are already possible. We have no choice at present."* - Anthony, father of a daughter living with GAMT deficiency

Medication side effects are a concern. Individuals who have long QT syndrome are unable to take some types of medications, and some medications can make the symptoms worse.

> *"You're playing 'whack-a-mole' every day with symptoms that keep popping up. And, a lot of times the more you try to manage symptoms you are inadvertently creating new symptoms and experiencing side effects with some of these medicines, especially the seizure meds and antipsychotics. We are having to make difficult choices on what is the lesser of the evils and unfortunately it's all at the expense of our children."* - Whitnie, caregiver for an individual living with CTD

> *"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_C. … So that's been a concern for us."* - Brittany, mother of a three-year-old boy living with CTD

Other treatment drawbacks.

Other drawbacks selected in the poll include **limited availability or accessibility of treatments**. Apart from the total lack of treatments for CCDS, other availability/accessibility issues mentioned throughout the report included a lack of trained and experienced therapists, and patients in rural locations having to travel long distances for therapy. Several parents described how they were better able to access therapies and services through an autism diagnosis rather than a CCDS diagnosis.

Other treatment drawbacks and barriers to care not mentioned in the polls but discussed at the meeting include the **unexpected CTD presentation in females, challenges of treating patients who have communication issues and intellectual disabilities**, **the large amount of blood draws required for monitoring**, **challenges with obtaining MRIs, and a fear of doctors**.

Poll Question 9

CCDS families need cures and treatments that work.

Patients, parents and caregivers again used online polls to select their top three choices for what they would want in an ideal treatment for CCDS, short of a cure. One parent described how all of the poll choices are relevant and how they would change with time.

> "*Answering this last question, it depended on where you are in the journey and how old your child is. If I was having this discussion when he was four or five, I would say I want his intellectual abilities to be higher. ... But now, I am 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. So, I do think we would*

want all of these things that you have listed with a better treatment." - Beth, mother of 28-year-old son living with GAMT deficiency

The poll selections fell into two main categories: **improving CCDS symptoms** such as intellectual disability, speech and communication, independence in daily activities, behavior, seizures; **improving the medications**. Poll results are presented in **Appendix 5, Q9**.

REGISTRY REFLECTIONS: CreatineInfo Registry participants were asked to rank the five outcomes most important to them in a future CCDS treatment, in order of importance. The most frequently selected outcomes were: speech and communication (76%), learning difficulties (44%), seizures (41%), and focus and attention (39%).

Key Insight: Those living with CTD have an urgent, unmet need. Treatment for CTD is required. This point was echoed by many, many parents of those living with CTD.

"We still are desperately in need of an effective treatment for CTD. … A treatment for CTD would change the world not only for my son with the condition, but also for my healthy daughter and my husband and I as parents." - Jolene, mother of a child living with CTD

"Our kids deserve a treatment! Their lives are valuable. They deserve a treatment that will reduce the medical and behavioral stressors and problems they face due to CTD." - Karen, mother of two sons living with CTD

"A cure for Will at the age of 28 may improve his independence. But imagine a cure at the age of five and the impact and quality of life realized." - Melissa, mother of a 28-year-old son living with CTD

Key Insight: Existing treatments for AGAT and GAMT deficiencies are not always effective and are enormously difficult to administer. These patients need better treatments as well.

"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. … 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." - Christina, 20-year-old woman living with AGAT deficiency

"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." - Leif, father of a 13-year-old son living with GAMT deficiency

"Yes, outcomes are better for patients diagnosed at birth (like my son) but it's not enough. He would also benefit from a better treatment. Treatment for GAMT is not all buttoned up. We need and want better. We worry about the long term effects of his

elevated GAA and how this will affect him as an adult. We worry that our daughter will die in her sleep from SUDEP. We would participate in trials but they can't be placebo. We need a therapy right away." - Heidi, mother of a 19-year-old daughter and an 11-year-old son living with GAMT deficiency

Key Insight: CCDS is so devastating, even small improvements would make big differences for individuals and families with CCDS.

"Even the smallest improvements of quality of life for patients of CTD can have a monumental impact on their lives, day to day." - Gina, caregiver for an individual living with CTD

"CTD families are greatly suffering and desperate for some solution even if not perfect." - Rodolfo, caregiver of an individual living with CTD

"*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*." - Trey, father of a 19-year-old daughter and an 11-year-old son living with GAMT deficiency

Help with intellectual disability and improved speech and communication.

Short of a complete cure, CCDS families want a treatment to **help with intellectual disability** and **improve speech and communication**. These closely related improvements were the top two selections in the online poll.

"I see her every day in this dysfunctional body wanting to express herself, wanting to communicate like us. I ask you, please remember Daisy." - Susie, mother of a 21-year-old daughter living with GAMT deficiency

We need treatments for CTD now, not later, not in five years. NOW. Treatments need to focus on increasing cognitive abilities including increasing attention and focus." - Laura, mother of an eight-year-old son living with CTD

"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." - Kayla, mother of a four-year-old son with CTD

"*We need something that will get creatine into our kids' brains and help give them a chance of living normal, independent lives, and to be able to communicate their needs and ideas clearly. … We want to give him the best chance possible to achieve his full potential in life*." - Erin, mother of a 7-year-old son living with CTD

Greater independence in daily activities, including better toileting/self-care behaviors.

Greater independence in daily activities was the third choice selected in the polls, which includes **better toileting and self-care behaviors**, also listed as poll responses.

> *"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."* - Kayla, mother of a four-year-old son with CTD

> *"I would like my 4-year-old son to have a minimum of autonomy. I wish he could speak, be understood, be calmer. He is a golden boy who deserves a chance to live better."* - Thaluama, mother of a four-year-old son living with CTD

> *"Our 12-year-old son has CTD. We are hoping for a treatment or cure soon that will improve his independence and quality of life."* - Jason, father of a 12-year-old son living with CTD

> *"A treatment can hopefully reduce the chance of health issues in the future and will help him to develop some skill sets, start learning, start communicating and understanding others and many other things. Any improvement in his daily routine has a massive impact in his life and in our life as parents."* - Ashkan, parent of an eight-year-old son living with CTD

Better behavioral control.

Many parents would like a medication to relieve anxiety, and lessen reactive outbursts.

> "*A treatment for anxious behavior that causes aggression would be greatly appreciated. … There has to be a medicine that can be developed to help GAMT patients lessen their anxiety that causes outbursts."* - Beth, caregiver of an individual living with GAMT deficiency

> *"I don't expect a miracle. We know that our son will probably not catch up when it comes to intellectual disability or speech delay, and that seizures will not go away either. However, if our son would have less behavioural issues, wouldn't suffer from external stimuli that much, he would be able to enjoy life so much better. And so would we as parents."*- Kim, mother of a seven-year-old son living with CTD

> *"If we could see a reduction in the aggressive behaviors, self injury, sensory and feeding issues that prevent our children from being able to integrate into society and live independently without the need for 1:1 caregiver support, that would be a huge benefit and a big win for families and patients."* - Whitnie, caregiver for an individual living with CTD

Improved medication: Easier administration, improved taste, and a reduction in side effects.

This poll choice reflected all the treatment challenges that AGAT and GAMT families experience, which were well described previously in this report. They asked for better tasting supplements, pills instead of powders, and extended-release formulations.

> *"The current treatment includes the administering of supplements which have an unappealing taste. As the patient grows, the dosage increases leading to even more unpalatable supplementation. It would be great if other avenues of administering the supplements could be explored further."* - Carien, parent of a two-year-old son living with GAMT deficiency

> *"If managing the medication is difficult- weighing powders, carrying 90 pills for one day's dose, etc. then he is more likely to be inconsistent. Not taking his medication can lead to brain damage. He needs something easy to manage on his own."* - Missy, mother of a son living with GAMT

> *"It would be good to have some kind of [an extended-release formulation] that stays in their system."* - Beth, mother of 28-year-old son living with GAMT deficiency

REGISTRY REFLECTION: CreatineInfo Registry participants report that the two most important attributes of an oral medication are 1) manageable volume or quantity (75%) and 2) a neutral or desirable taste (73%).

Decreased seizures.

Families want to decrease seizures and GAMT families also want to reduce GAA levels.

> *"For us, ideal treatments for CCDS would … prevent life-threatening seizures. it would truly mean the world to a parent who has watched their child seize for 18 hours straight.*" - Nathan, father of three sons living with CTD

> *"We need a treatment that will lower her GAA. Lowering of GAA in many GAMT patients has correlated with reduction or stopping of seizures and improved outcomes."* - Heidi, mother of a 19-year-old daughter and an 11-year-old son living with GAMT deficiency

> *"I hope that with the future of treatment we would be able to control [seizures] without having to use anti-seizure medicines*." - Kim, mother of a 17-year-old son and a 13-year-old daughter living with GAMT deficiency

Other characteristics of an ideal CCDS treatment.

Other ideal CCDS treatment characteristics selected in the polls included **improved social interactions**, **better focus and attention** and **improved gross/fine motor skills**.

> *"Would like to see Adam thriving, hold a pen and write his name down, focused and able to read a book. When he is asked, to be able to say 'my name is Adam and I am four years old'*." - Abir, parent of a four-year-old son living with CTD
>
> "*Eli is 4 years old with CTD. I would love to see my son one day able to hold a pen properly, write his name, call my name, open a discussion with his sister and ride a bike or shoot a basketball*." - Michael, father of a four-year-old son living with CTD

Other characteristics of an ideal CCDS treatment for CCDS not captured in the polls included having treatments that would **better manage weight gain** and **was affordable for all**.

Additional important CCDS priorities identified during the EL-PFDD.

During the meeting discussion, CCDS families identified other CCDS priorities and needs.

- More widespread knowledge about CCDS in the medical profession.
- More widespread medical knowledge and research is needed with regards to the identification and treatment of women with CTD.
- GAMT families need a way to monitor GAA, and more evidence for the efficacy of low protein diets.
- Parents would like to find better ways to evaluate whether medications and treatments are working, including more appropriate clinical trial endpoints other than motor symptom improvements.
- Parents would like wider adoption of GAMT newborn screening, as well as AGAT and CTD newborn screening.
- Many are enthusiastic about participating in clinical trials as long as safety is not a concern. Placebo-controlled trials are not an option.
- Parents emphasized the need to identify clinical trial endpoints that are meaningful for patients and their families.

> *"Too many end points are designed and validated around motor skills, but motor skills are NOT critical in CTD so let's not measure something because we can, let's measure what matters*." - Laura, mother of an eight-year-old son living with CTD

Incorporating Patient Input into a Benefit-Risk Assessment Framework

The CCDS EL-PFDD meeting helped to increase the understanding of how CCDS impact patients and their loved ones, and reinforced the urgent need for effective therapeutics for these disorders.

Table 1 speaks to the challenges of having a lifelong disease burden that CCDS patients endure. It serves as the proposed introductory framework for the Analysis of Condition and Current Treatment Option to be adapted and incorporated in the FDA's Benefit-Risk Assessment. This may enable a more comprehensive understanding of these disorders for key reviewers in the FDA Centers and Divisions who would be evaluating new treatments for CCDS.

The information presented captures the perspectives of patients and families living with CCDS presented at the January 24, 2023 EL-PFDD. The collective hope of CCDS families is that data resulting from this meeting will help inform the development of CCDS-specific, clinically meaningful endpoints for current and future clinical trials, as well as encourage researchers and industry to investigate better treatments.

Note that the information in this sample framework is likely to evolve over time.

TABLE: Benefit-Risk Table for CCDS – CTD, GAMT deficiency, AGAT deficiency

	EVIDENCE AND UNCERTAINTIES	CONCLUSIONS AND REASONS
ANALYSIS OF CONDITION / IMPACTS ON ACTIVITIES OF DAILY LIVING	**For many, CCDS is diagnosed too late.** Diagnosis is traumatic and very little information is available about these disorders. Parents of children diagnosed with CTD expressed that at the time of their child's diagnosis, they were horrified to learn that there are no treatments available. **Early diagnosis for GAMT and AGAT deficiencies makes a world of difference**. Supplementation with creatine monohydrate and other amino acids can prevent some symptoms. Many children with GAMT or AGAT deficiencies are not diagnosed and treated early enough to prevent neurological damage. **Individuals living with CCDS experience many health concerns.** Speech impairment, developmental delay, and intellectual disability are the most troublesome CCDS health concerns, followed by seizures, behavior issues, and a long list of other symptoms. Symptoms tend to be more severe in individuals living with CTD; the longer individuals with GAMT or AGAT go without supplementation, the more severe their symptoms can be.	**CCDS has an enormous disease burden.** All activities of daily life are impacted, and families suffer. The inability to communicate effectively makes individuals living with CCDS vulnerable. Challenges with toileting/self-care, self-regulation, and completing tasks compromise independence. Behavioral issues limit participation in society, and isolation is common for patients and their entire families. **Parents have many worries for their loved ones' future.** They worry about who will care for their loved one after they pass, whether their loved one will ever live independently, if their symptoms will get worse, and if new symptoms will appear. They also worry about their own physical and mental health.
CURRENT TREATMENT OPTIONS/ PROSPECTS FOR FUTURE TREATMENTS	**There are no FDA approved treatments for CCDS.** All individuals living with CCDS require a large number of different medications, supplements, and medical consults to address the symptoms of the disease, as parents will try anything possible to make a difference in the lives of their children. Most individuals living with CCDS require a great deal of supports including speech, occupational, and physical therapy as well as school adaptations. **Current CCDS treatment approaches and therapies are ineffective and require enormous effort and time commitments.**	**Individuals living with CTD have an urgent unmet need for effective treatments. Existing treatments for AGAT and GAMT deficiencies are not always effective and are enormously difficult to administer.** **CCDS families need treatments that work**. All CCDS are in dire need of therapies to manage symptoms, prevent further deterioration and improve quality of life. CCDS are so devastating, even small improvements would make big differences for individuals and families. Improvements are needed for medication taste and administration. Medical knowledge of CCDS must be improved.
	See the Voice of the Patient report for a more detailed narrative.	

Appendix 1: CCDS EL-PFDD Meeting Agenda

January 24, 2023 - 10:00 AM-3:15 PM EST

10:00 – 10:05AM	Welcome and Opening Remarks: *Heidi Wallis, Executive Director, Association for Creatine Deficiencies (ACD)*
10:05 – 10:15 AM	FDA Remarks - The Role of Patients in Drug Development: *Dr. Anna Choe, Division of Rare Diseases and Medical Genetics, CDER, FDA*
10:15 – 10:30AM	Clinical Overview of CCDS: *Dr. Andreas Schulze, The Hospital for Sick Children*
10:30 – 10:35AM	Overview of Discussion Format: *Larry Bauer, Hyman, Phelps, & McNamara Meeting moderator*
10:35 – 10:40AM	Audience Demographic Polling Questions

Morning Session: Living with CCDS - Symptoms and Daily Impacts

10:40 – 11:10AM	Panel 1: Patient & caregiver perspectives on symptoms and daily impacts - 6 pre-recorded panelists including 1 AGAT, 2 GAMT and 3 CTD
11:10 – 12:30PM	Audience discussion and remote polling on Topic 1 including: five discussion starters (3 CTD, 2 GAMT), audience remote polling and moderated audience discussion (call in and write in)
12:30 – 1:00PM	Break

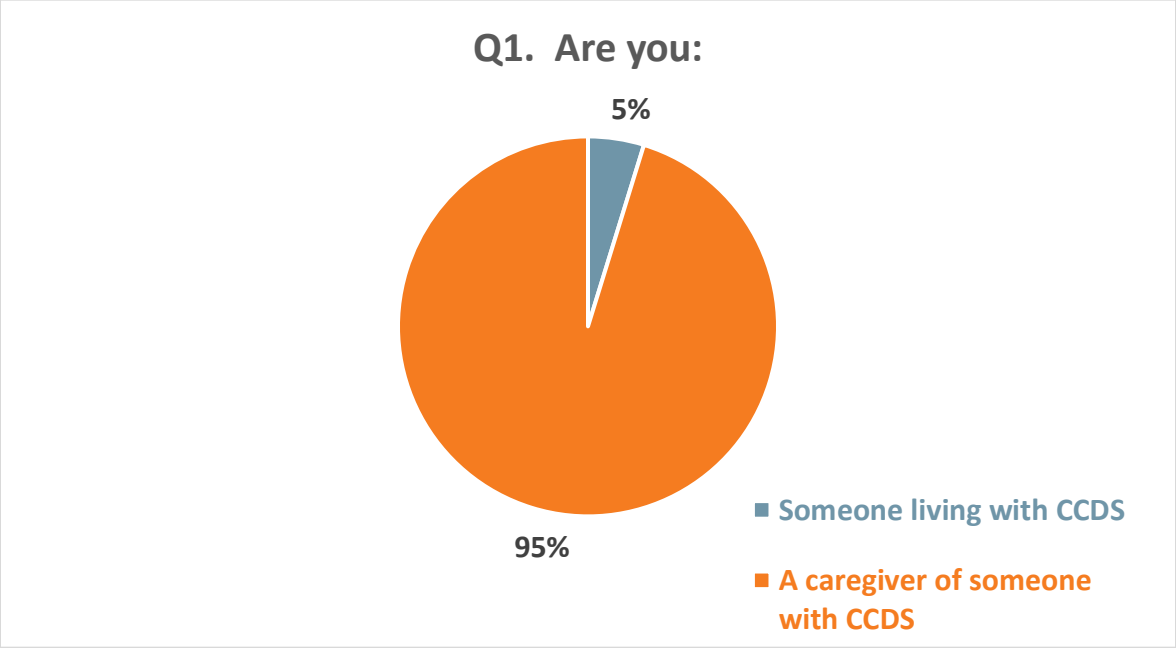
Afternoon Session: Current & Future Approaches to Treatment for CCDS

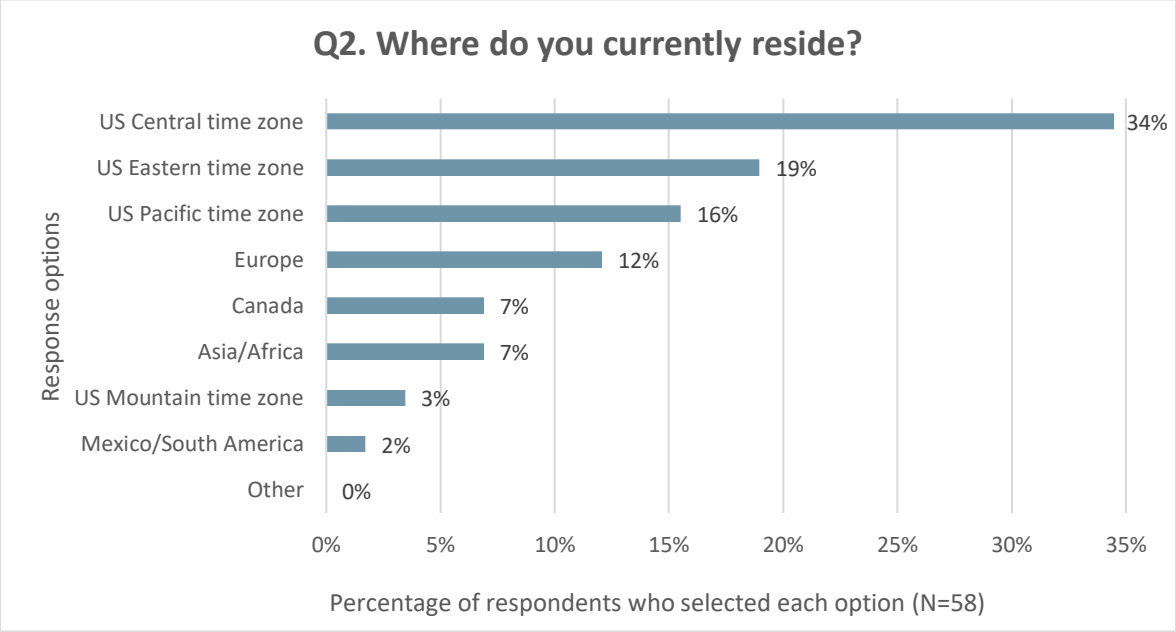
1:00 – 1:05PM	Introduction to Session 2: *Heidi Wallis, ACD*
1:05 – 1:15PM	Overview of treatments: *Dr. Nicola Longo, University of Utah*
1:15 – 1:45PM	Panel 2: Patient & caregiver perspectives on current and future treatments – 6 pre-recorded panelists including 1 AGAT, 2 GAMT and 3 CTD
1:45 – 3:00PM	Audience discussion and remote polling on Topic 2 including: five discussion starters (3 CTD, 2 GAMT), audience remote polling and moderated audience discussion (call in and write in)
3:00 – 3:10PM	Meeting Summary: *Sangeetha Iyer, PhD., ACD Scientific Advisor*
3:10 – 3:15PM	Wrap Up and Thank You: *Heidi Wallis, ACD*

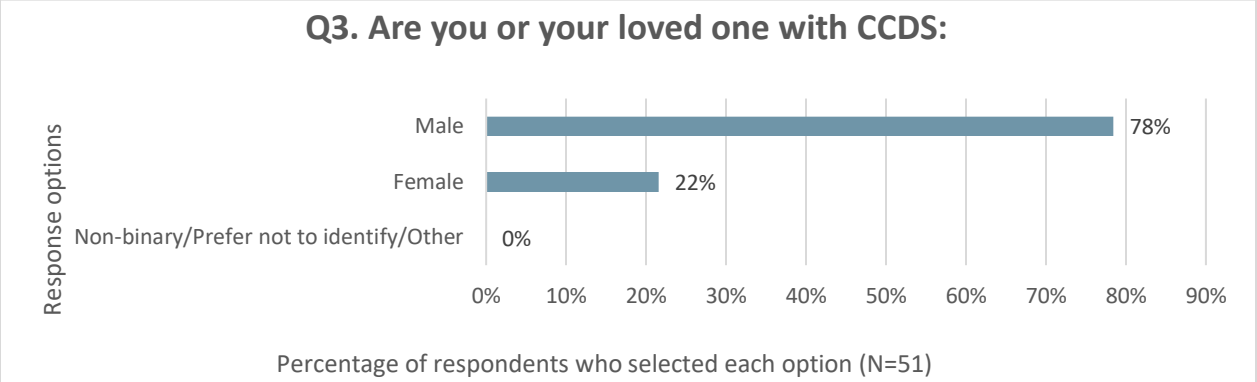
Appendix 2: Meeting demographics

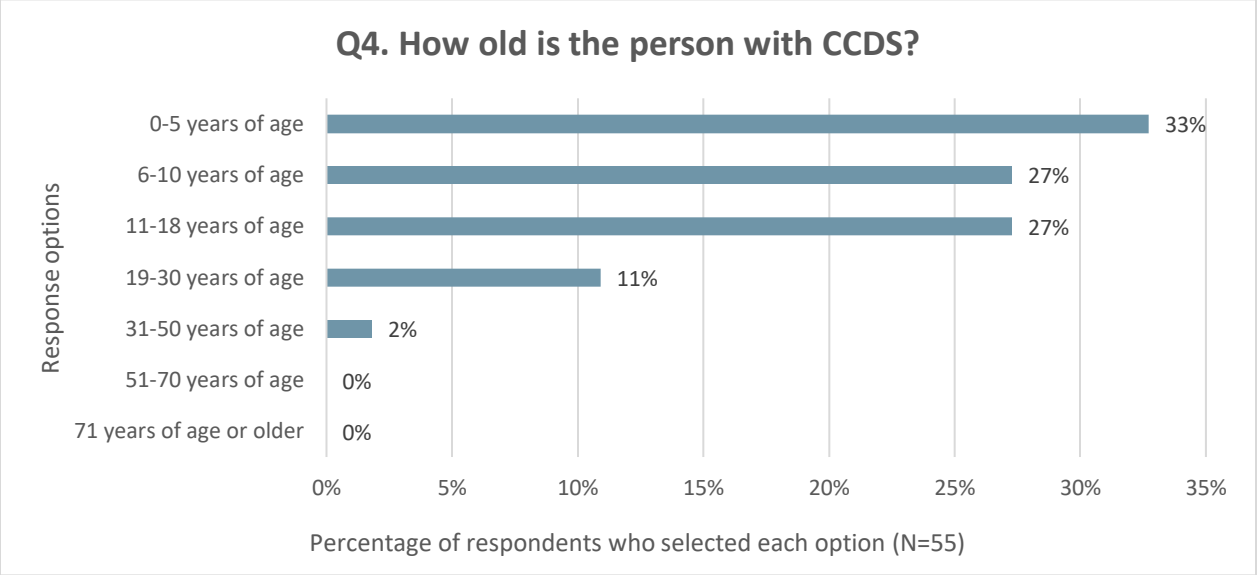
The graphs below include patients, parents, and caregivers who chose to participate in online polling at the January 24, 2023 meeting. The number of individuals who responded to each polling question is shown below on the X axis (N=x).

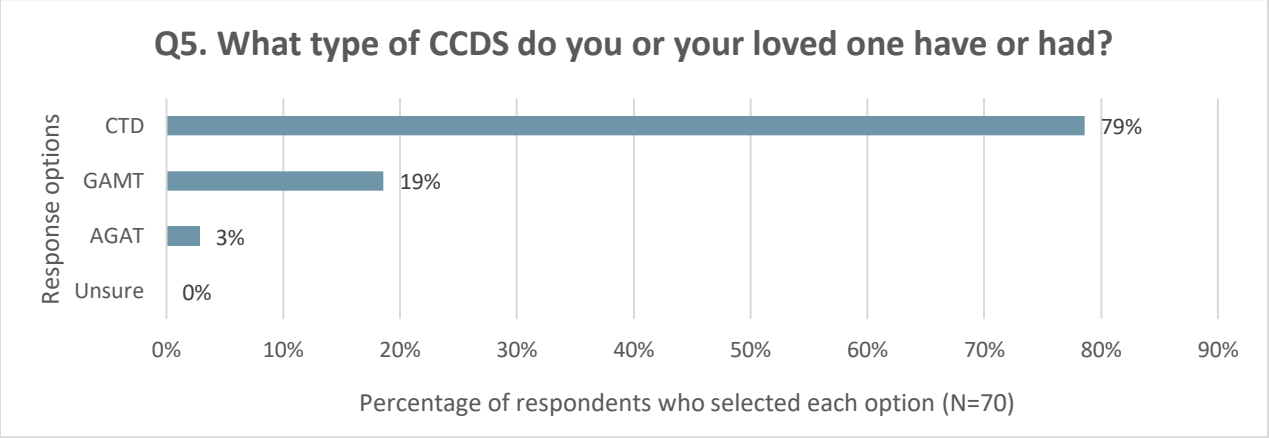
While the response rates for these polling questions is not considered scientific data, it provides a snapshot of those who participated in the CCDS EL-PFDD meeting. Note that meeting demographics are dynamic and may have changed as more individuals joined the meeting.






Q3. Are you or your loved one with CCDS:
Response options
Male
Female
Non-binary/Prefer not to identify/Other
78%
22%
0%
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
Percentage of respondents who selected each option (N=51)


Q4. How old is the person with CCDS?
Response options
0-5 years of age
6-10 years of age
11-18 years of age
19-30 years of age
31-50 years of age
51-70 years of age
71 years of age or older
33%
27%
27%
11%
2%
0%
0%
0%
5%
10%
15%
20%
25%
30%
35%
Percentage of respondents who selected each option (N=55)


Q5. What type of CCDS do you or your loved one have or had?
Response options
CTD
GAMT
AGAT
Unsure
79%
19%
3%
0%
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
Percentage of respondents who selected each option (N=70)

Appendix 3: Meeting Discussion Questions

Topic 1: Living with CCDS: Symptoms and Daily Impacts

1. Of all the symptoms and health effects of CCDS, which 1-3 symptoms have the most significant impact on you or your loved one's life?

2. How does CCDS affect you or your loved one on best and on worst days? Describe your best days and your worst days.

3. How has your or your loved one's symptoms changed over time? How has their ability to cope with the symptoms changed over time?

4. 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?

5. What do you fear the most as your loved one gets older? What worries you most about your loved one's condition?

Topic 2: Perspective on Current and Future Approaches to Treatment

1. What are you currently doing to manage you or your loved one's CCDS symptoms?

2. How well do these treatments treat the most significant symptoms and health effects of CCDS?

3. What are the most significant downsides to you or your loved one's current treatments and how do they affect daily life?

4. Short of a complete cure, what specific things would you look for in a treatment for CCDS? What factors would be important in deciding whether to use a new treatment?

Appendix 4: Meeting Panelists and Callers

Session 1: Pre-recorded panelists

- Whitnie, parent of a 12-year-old son living with CTD
- Kimberly, mother of a 22-year-old daughter living with CTD
- James, father of a six-year-old boy living with CTD
- Jenny, mother of a 20-year-old daughter living with AGAT deficiency
- Jerry, parent of two children, aged 18 and 14, living with GAMT deficiency
- Glenda, parent of a 23-year-old woman living with GAMT deficiency

Session 1: Live panelists

- Celine, mother of a 16-year-old boy living with CTD
- Rachel, mother of an 11-year-old boy living with CTD
- Carole, mother of a 32-year-old woman with CTD, diagnosed at the age of 16
- Beth, mother of an 18-year-old son and a 14-year-old daughter living with GAMT deficiency
- Trey, father of a 19-year-old daughter and an 11-year-old son living with GAMT deficiency

Session 1: Callers

- Brittany, parent of a three-year-old boy living with CTD
- Regina, caregiver of a 28-year-old daughter and a nine-year-old grandson, both living with CTD
- Celeste, mother of an 11-year-old son living with CTD
- Laura, mother of an eight-year-old son living with CTD

Session 2: Pre-recorded panelists

- Susie, mother of a 21-year-old daughter living with GAMT deficiency
- Leif, father of a 13-year-old son living with GAMT deficiency
- Christina, 20-year-old woman living with AGAT deficiency
- Christina and Zigmas, parents of a 13-year-old daughter living with CTD
- Kayla, mother of a four-year-old son living with CTD
- Nathan, father of three sons living with CTD

Session 2: Live panelists

- Beth, mother of 28-year-old son living with GAMT deficiency
- Gina, mother of a 16-year-old son living with CTD
- Regina, caregiver of a 28-year-old daughter and a nine-year-old grandson, both living with CTD
- Christina, mother of four-year-old daughter and two-year-old son living with GAMT deficiency

- Dan, father of a seven-year-old son living with CTD

Session 2: Callers

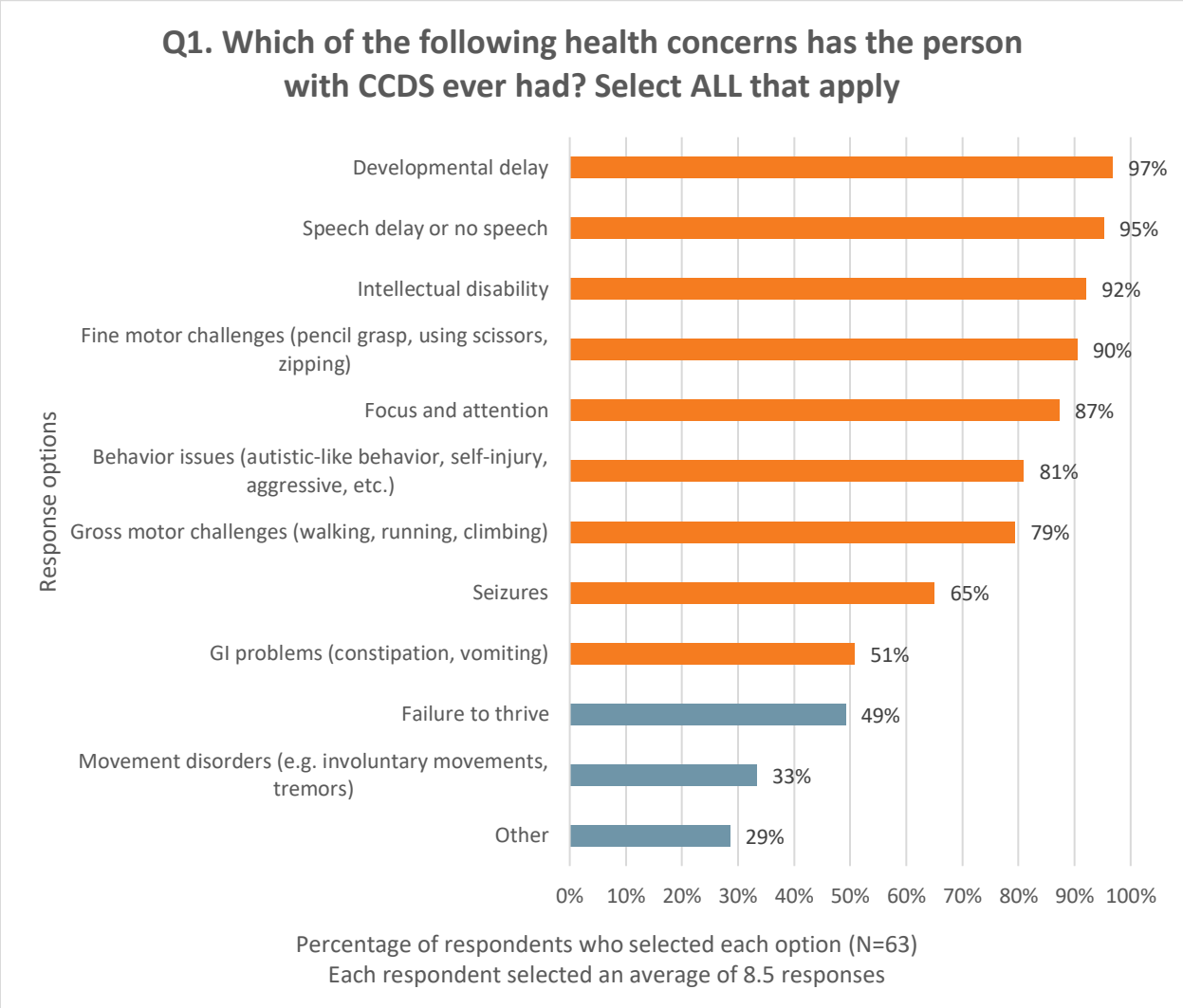
- Brittany, mother of a three-year-old boy living with CTD
- Celeste, mother of an 11-year-old son living with CTD
- Jolene, mother of a child living with CTD
- Kim, mother of a 17-year-old son and a 13-year-old daughter living with GAMT
- Randy, father of a five-year-old child living with CTD

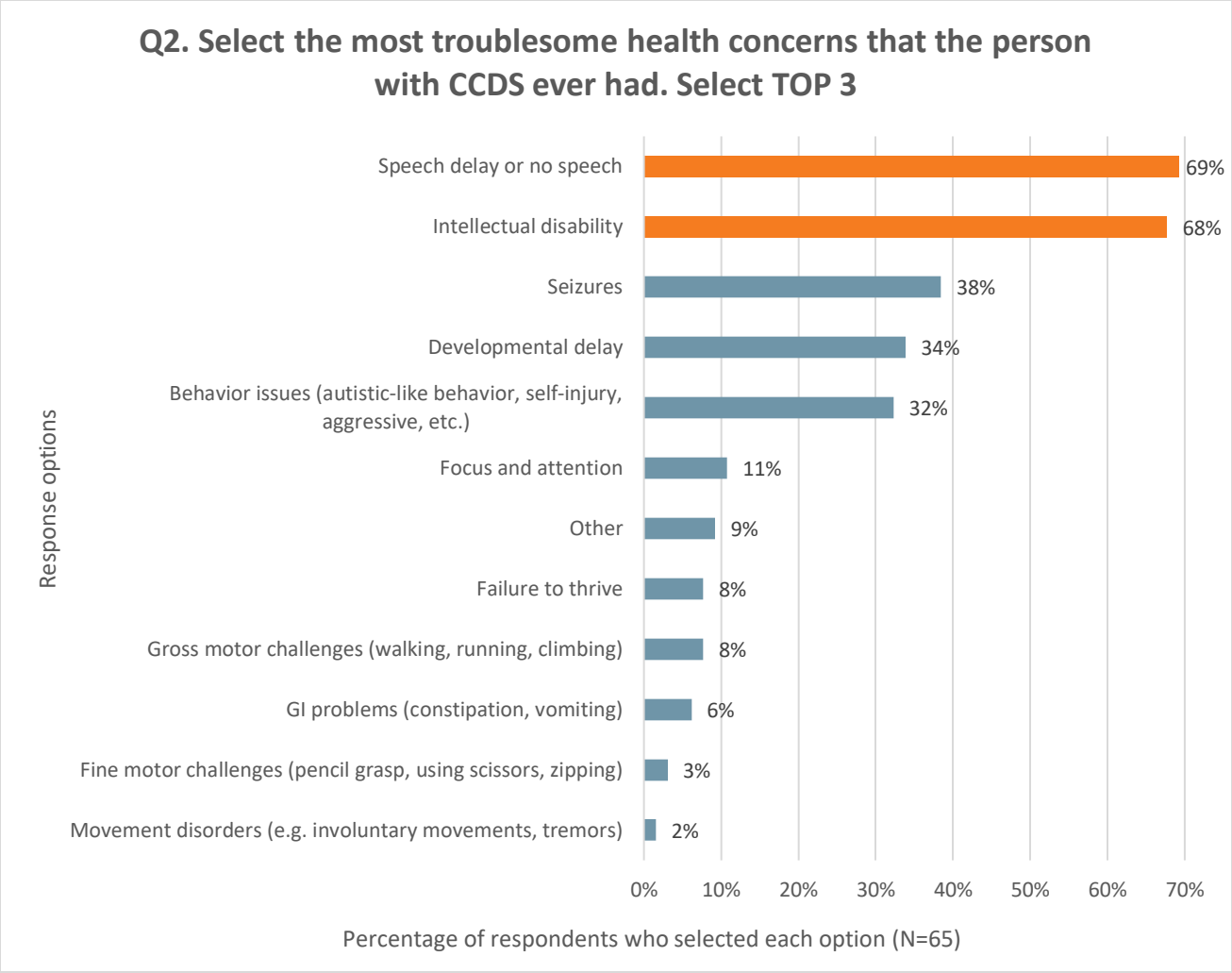
Appendix 5: Online Meeting Poll Responses

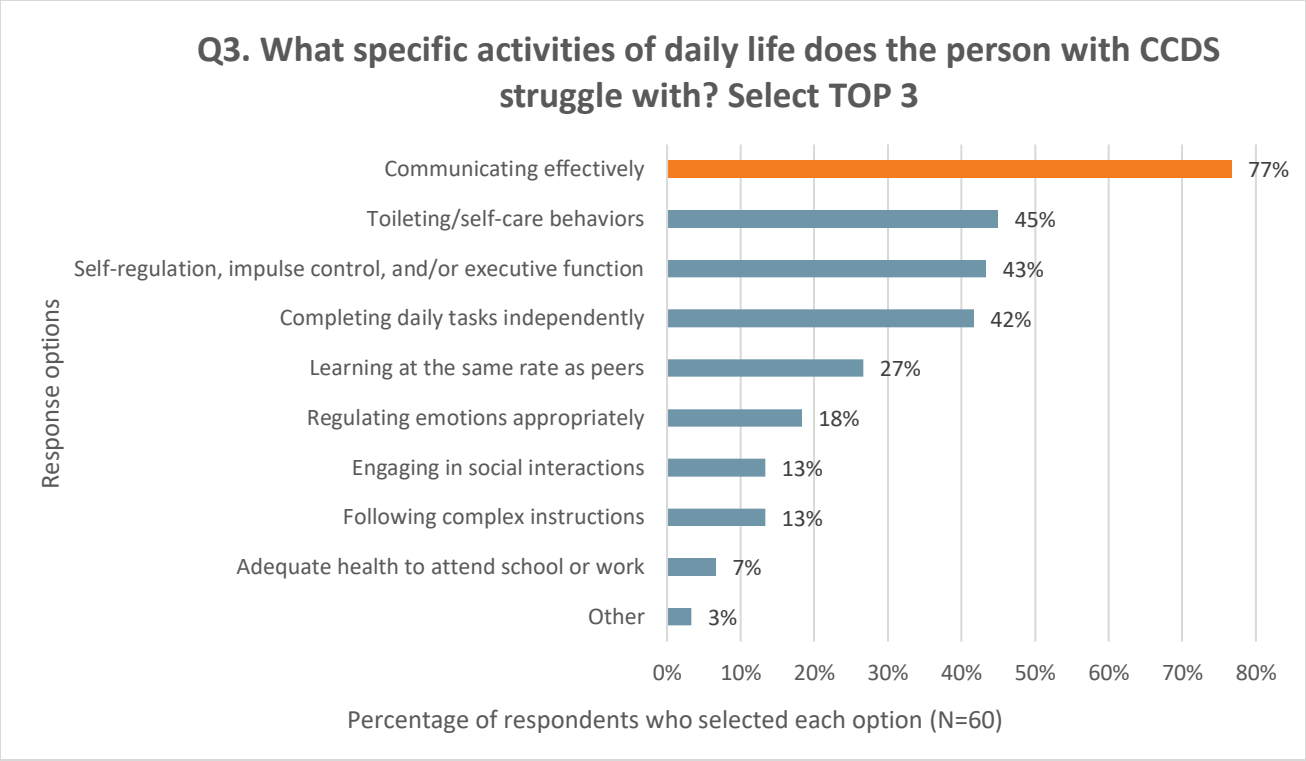
The graphs below include patients, parents, and caregivers who chose to participate in online polling. The number of individuals who responded to each polling question is shown below on the X axis (N=x).

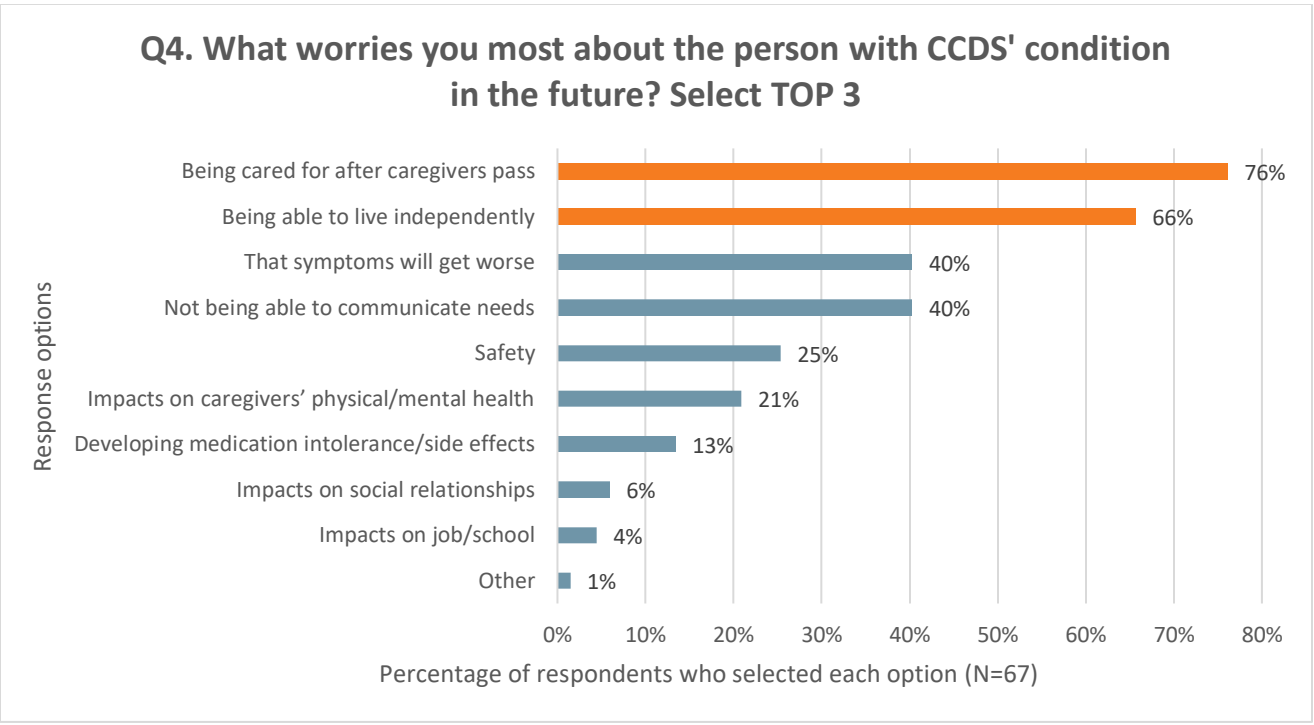
The responses for these polling questions are not considered scientific data. These are intended to complement the patient comments made during and after the meeting.

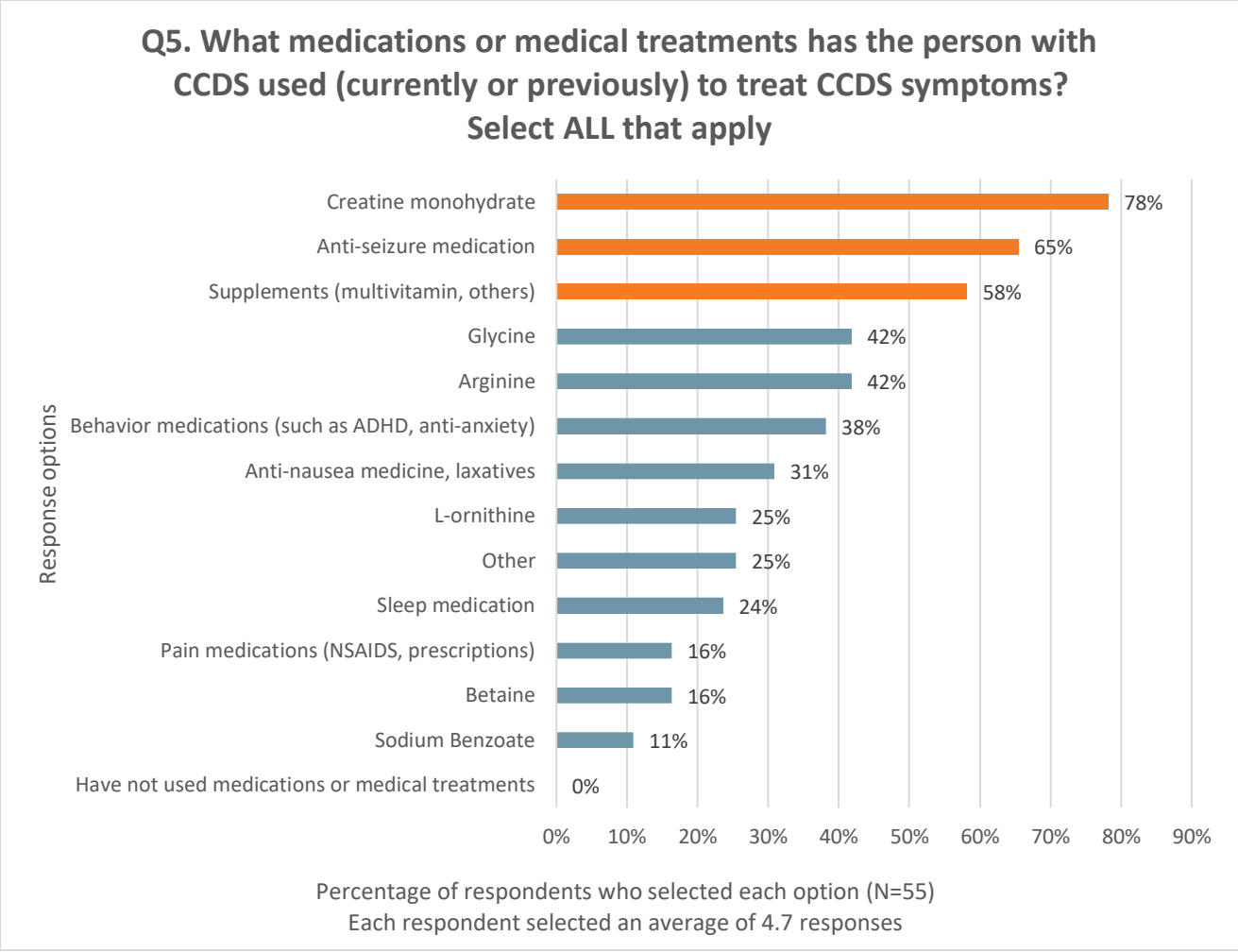
Poll responses selected by more than 50% of voters are shown in **orange**.

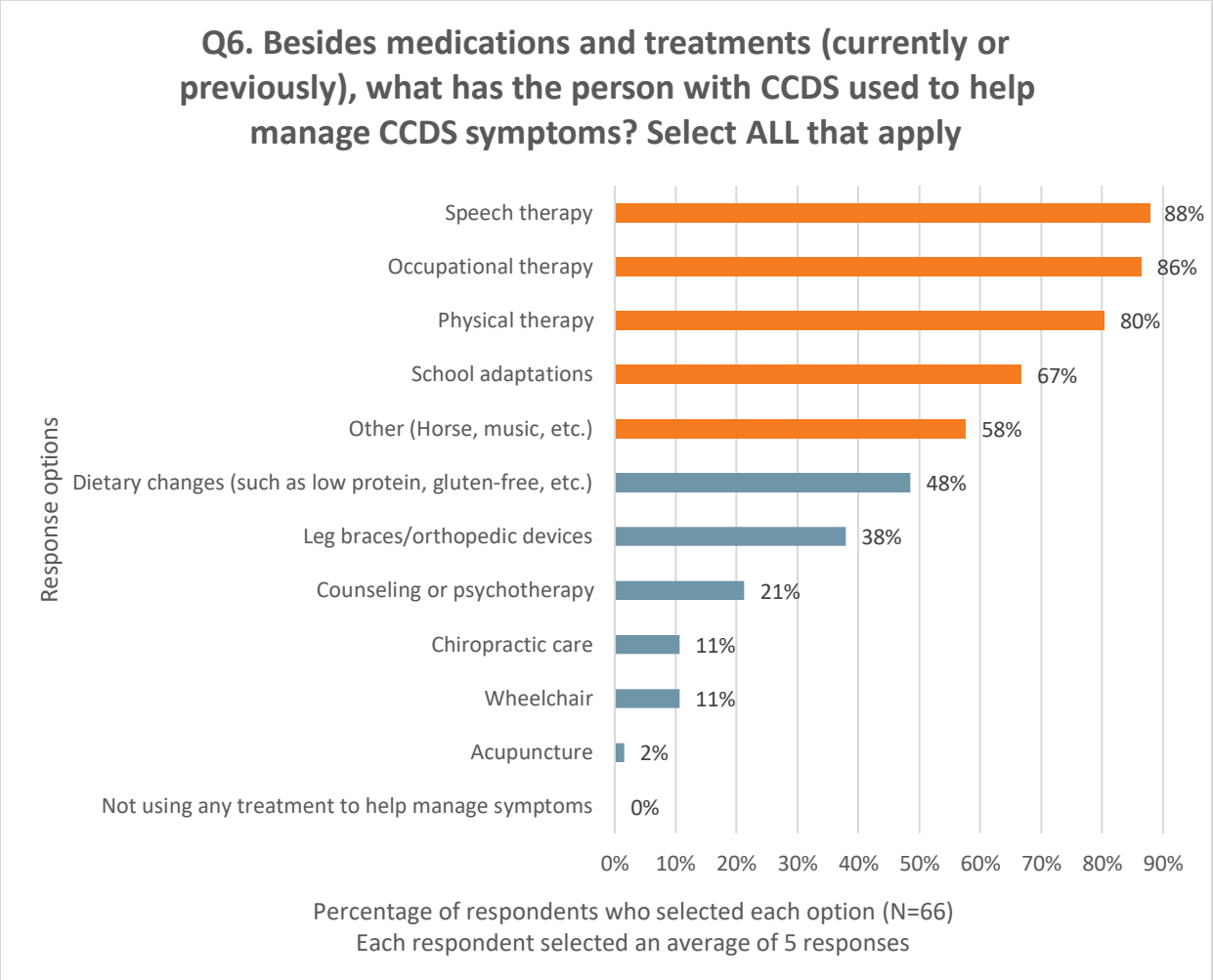


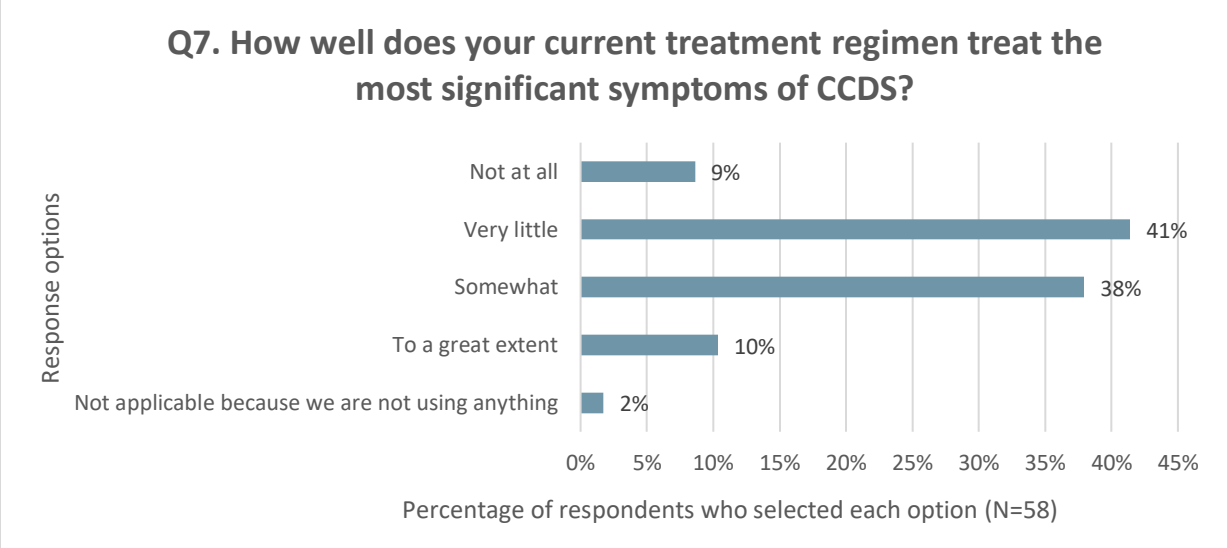

Q2. Select the most troublesome health concerns that the person with CCDS ever had. Select TOP 3
Response options
Speech delay or no speech
69%
Intellectual disability
68%
Seizures
38%
Developmental delay
34%
Behavior issues (autistic-like behavior, self-injury, aggressive, etc.)
32%
Focus and attention
11%
Other
9%
Failure to thrive
8%
Gross motor challenges (walking, running, climbing)
8%
GI problems (constipation, vomiting)
6%
Fine motor challenges (pencil grasp, using scissors, zipping)
3%
Movement disorders (e.g. involuntary movements, tremors)
2%
0%
10%
20%
30%
40%
50%
60%
70%
Percentage of respondents who selected each option (N=65)

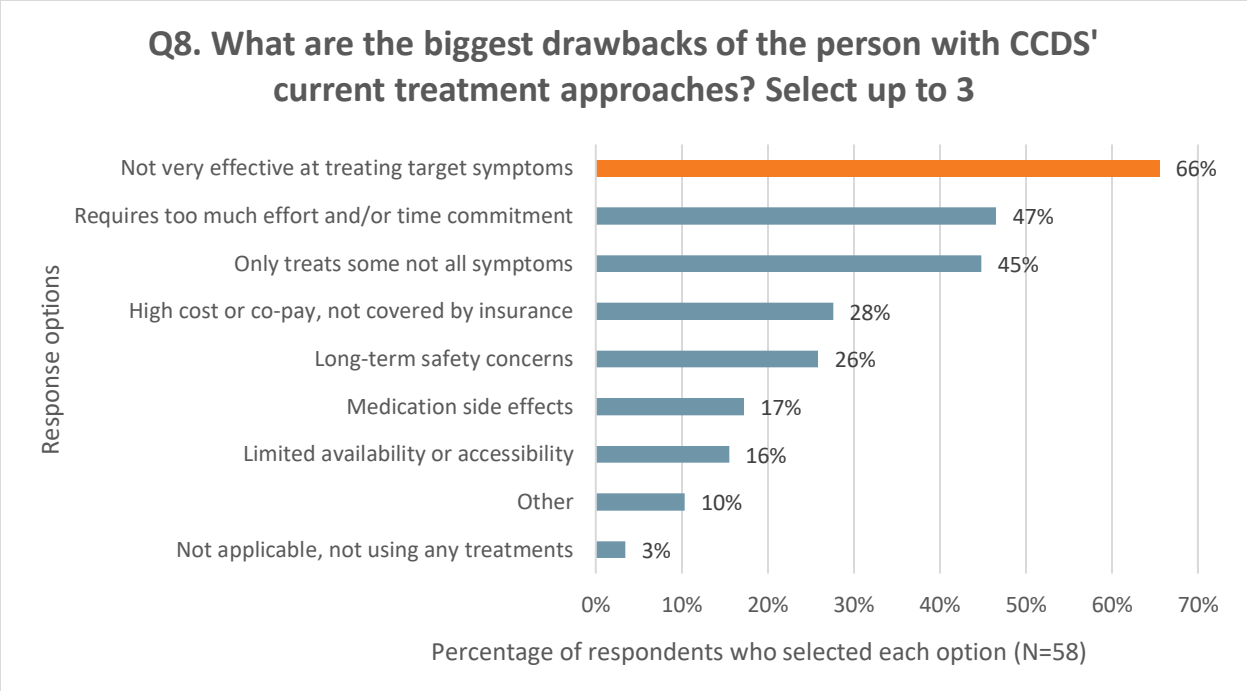

Q3. What specific activities of daily life does the person with CCDS struggle with? Select TOP 3
Response options
Communicating effectively
Toileting/self-care behaviors
Self-regulation, impulse control, and/or executive function
Completing daily tasks independently
Learning at the same rate as peers
Regulating emotions appropriately
Engaging in social interactions
Following complex instructions
Adequate health to attend school or work
Other
77%
45%
43%
42%
27%
18%
13%
13%
7%
3%
0%
10%
20%
30%
40%
50%
60%
70%
80%
Percentage of respondents who selected each option (N=60)

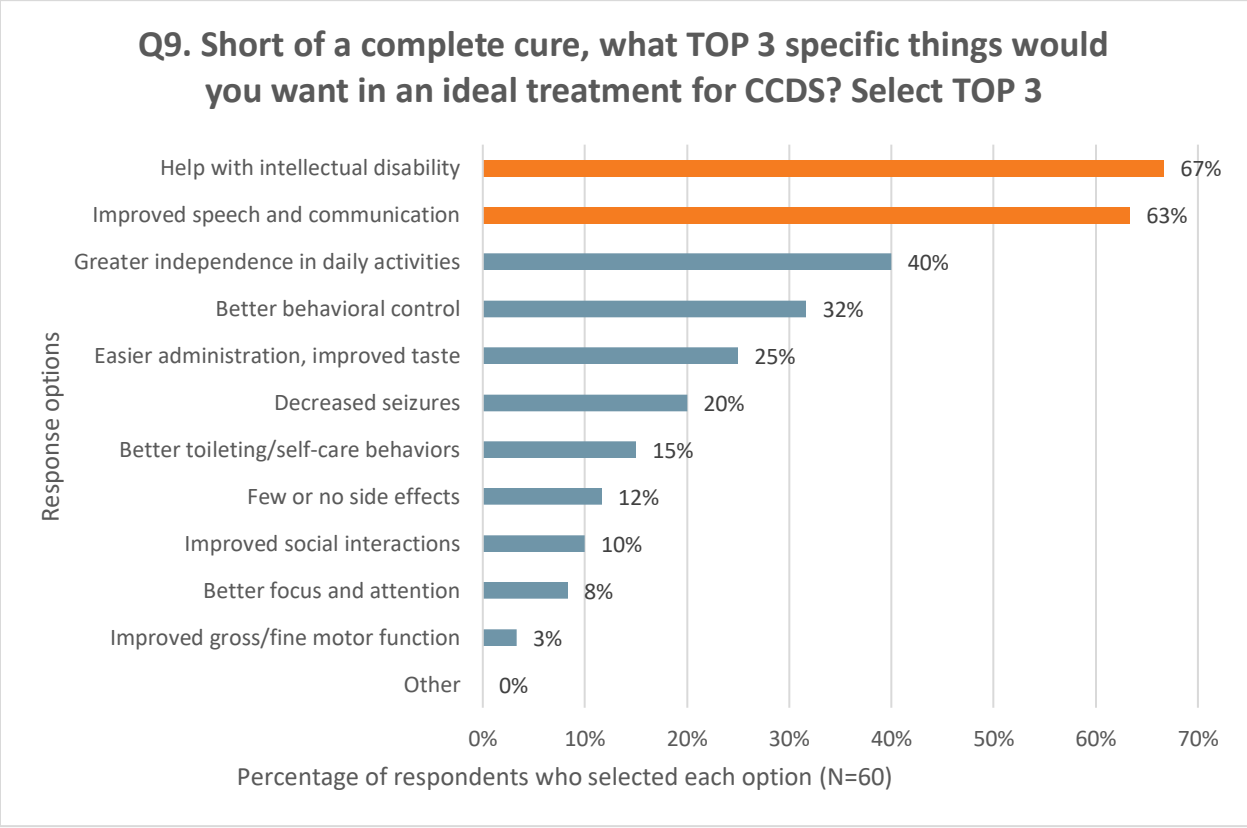

Q4. What worries you most about the person with CCDS' condition in the future? Select TOP 3
Response options
Being cared for after caregivers pass
Being able to live independently
That symptoms will get worse
Not being able to communicate needs
Safety
Impacts on caregivers' physical/mental health
Developing medication intolerance/side effects
Impacts on social relationships
Impacts on job/school
Other
76%
66%
40%
40%
25%
21%
13%
6%
4%
1%
0%
10%
20%
30%
40%
50%
60%
70%
80%
Percentage of respondents who selected each option (N=67)


Q5. What medications or medical treatments has the person with CCDS used (currently or previously) to treat CCDS symptoms? Select ALL that apply
Response options
Creatine monohydrate
Anti-seizure medication
Supplements (multivitamin, others)
Glycine
Arginine
Behavior medications (such as ADHD, anti-anxiety)
Anti-nausea medicine, laxatives
L-ornithine
Other
Sleep medication
Pain medications (NSAIDS, prescriptions)
Betaine
Sodium Benzoate
Have not used medications or medical treatments
78%
65%
58%
42%
42%
38%
31%
25%
25%
24%
16%
16%
11%
0%
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
Percentage of respondents who selected each option (N=55)
Each respondent selected an average of 4.7 responses


Q6. Besides medications and treatments (currently or previously), what has the person with CCDS used to help manage CCDS symptoms? Select ALL that apply
Response options
Speech therapy
Occupational therapy
Physical therapy
School adaptations
Other (Horse, music, etc.)
Dietary changes (such as low protein, gluten-free, etc.)
Leg braces/orthopedic devices
Counseling or psychotherapy
Chiropractic care
Wheelchair
Acupuncture
Not using any treatment to help manage symptoms
88%
86%
80%
67%
58%
48%
38%
21%
11%
11%
2%
0%
0% 10% 20% 30% 40% 50% 60% 70% 80% 90%
Percentage of respondents who selected each option (N=66)
Each respondent selected an average of 5 responses


Q7. How well does your current treatment regimen treat the most significant symptoms of CCDS?
Response options
Not at all
Very little
Somewhat
To a great extent
Not applicable because we are not using anything
9%
41%
38%
10%
2%
0% 5% 10% 15% 20% 25% 30% 35% 40% 45%
Percentage of respondents who selected each option (N=58)


Q8. What are the biggest drawbacks of the person with CCDS' current treatment approaches? Select up to 3
Response options
Not very effective at treating target symptoms
Requires too much effort and/or time commitment
Only treats some not all symptoms
High cost or co-pay, not covered by insurance
Long-term safety concerns
Medication side effects
Limited availability or accessibility
Other
Not applicable, not using any treatments
66%
47%
45%
28%
26%
17%
16%
10%
3%
0%
10%
20%
30%
40%
50%
60%
70%
Percentage of respondents who selected each option (N=58)


Q9. Short of a complete cure, what TOP 3 specific things would you want in an ideal treatment for CCDS? Select TOP 3
Response options
Help with intellectual disability
Improved speech and communication
Greater independence in daily activities
Better behavioral control
Easier administration, improved taste
Decreased seizures
Better toileting/self-care behaviors
Few or no side effects
Improved social interactions
Better focus and attention
Improved gross/fine motor function
Other
67%
63%
40%
32%
25%
20%
15%
12%
10%
8%
3%
0%
0%
10%
20%
30%
40%
50%
60%
70%
Percentage of respondents who selected each option (N=60)

Appendix 6: The CreatineInfo Patient Registry and Natural History Study

The CreatineInfo Patient Registry and Natural History Study for Cerebral Creatine Deficiency Syndromes (CCDS) is a patient-reported registry and natural history study created by the Association for Creatine Deficiencies (ACD) and hosted by the National Organization for Rare Disorders (NORD). This registry collects longitudinal data on individuals living with CCDS, including socio-demographic, diagnostic, management of care, and treatment and disease progression. It has the potential to inform and accelerate research focusing on what is most meaningful to patients and caregivers, and it will continue to engage and empower the CCDS community to be active partners in shaping the CCDS research agenda.

To learn more, please visit **https://creatineinfo.iamrare.org/**.