

# The Voice of the Patient Report: CDKL5 Deficiency Disorder (CDD)

A report on the Externally Led Patient-Focused Drug Development Meeting corresponding to FDA's  
Patient-Focused Drug Development Initiative

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Hosted by:  
Loulou Foundation  
International Foundation for CDKL5 Research

Submitted to:  
Center for Drug Evaluation and Research (CDER) &  
Center for Biologic Evaluation and Research (CBER)  
U.S. Food and Drug Administration (FDA)



## **The Voice of the Patient: CDKL5 Deficiency Disorder**

This document represents a comprehensive summary report composed by patient advocacy organizations as a result of an externally led patient-focused drug development meeting; a parallel effort to FDA's Patient-Focused Drug Development Initiative. This report reflects the organization's account of the perspectives of patients and caregivers who participated in the public meeting.

Submitted to:

Center for Drug Evaluation and Research (CDER) &

Center for Biologic Evaluation and Research (CBER)

U.S. Food and Drug Administration (FDA)

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## Introduction

On November 1, 2019, the Loulou Foundation and the International Foundation for CDKL5 Research (IFCR) hosted an externally-led patient-focused drug development (EL-PFDD) meeting to share the perspectives of caregivers representing children with CDKL5 deficiency

*“Please see us for our potentials, not our symptoms and limitations”*

disorder (CDD—colloquially referred to as ‘CDKL5’ by some community members), its impact on their daily lives, and their expectations and priorities for current and future treatments with senior officials at U.S. Food and Drug Administration (FDA), the pharmaceutical industry, academia and research institutions. The meeting was as an expansion of and modeled after the agency’s meetings under the Patient-Focused Drug Development initiative, an FDA commitment under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) to more systemically gather caregiver and patients’ perspectives on their condition and available therapies to treat their condition. In addition, the recently passed 21st Century Cures Act has emphasized the importance of caregiver and patient input in the regulatory process, mandating that regulators describe what information they have about patient and caregiver experiences and preferences to inform decisions about which outcome measures matter to those most affected and to consider how they weigh the balance of risks and benefits of a particular treatment.

More information on the FDA Patient-Focused Drug Development meetings can be found at: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm347317.htm>.

## Overview of CDKL5 deficiency disorder

Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder is a rare and often profound neurodevelopmental encephalopathy caused by pathogenic alterations in the CDKL5 gene and a deficiency of functional CDKL5 protein. Variations in the CDKL5 gene were first linked with human disease in 2004 through cohorts of patients seen in Rett syndrome clinics who were found not to have alterations in the Rett gene, MeCP2 (methyl CpG binding protein 2). However, CDD is not Rett syndrome or even a variant of Rett, but a unique and complex disorder characterized by early onset and refractory epilepsy and severe developmental delays affecting motor, cognitive, behavioral and physical function. Depending on the individual, these impairments can also lead to gastrointestinal, musculoskeletal, cortical visual and autonomic conditions that range in severity and can be debilitating.

An X-linked disorder, CDD has been found in girls about four times more commonly than boys—as many male fetuses without a normal CDKL5 gene do not survive to birth.<sup>1</sup> Recent studies have determined a birth incidence of disease-causing CDKL5 mutations in one in 41,000 births.<sup>2</sup> At present, several hundred (under 1,000) individuals with CDD in the world are known to patient registries—however, diagnosis is

<sup>1</sup> Olson HE, Demarest ST, Pestana-Knight EM, et al., Cyclin-Dependent Kinase-Like 5 Deficiency Disorder: Clinical Review, *Pediatric Neurology*. in press. <https://doi.org/10.1016/j.pediatrneurol.2019.02.015>.

<sup>2</sup> Symonds JD, Zuberi SM, Stewart K, et al. Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort. *Brain*. 2019 Aug 1;142(8):2303-2318. doi: 10.1093/brain/awz195.

dependent upon access to genetic screening. Current estimates of prevalence at one referral center in the United States suggests that CDD may be found in about one in 75,000, representing less than 4,500 individuals with CDD in the U.S.<sup>3</sup>

## CDD pathogenesis

The role and function of the CDKL5 protein, a kinase that is highly expressed in the brain (localized to the nucleus of neurons and to synapses), is still emerging but it appears to have critical roles in the establishment of neural circuits and synaptic signaling. Evidence suggests that, in the nucleus, it phosphorylates DNMT1 (DNA methyltransferase 1), a protein involved in DNA methylation, and, in the synapses, phosphorylates EB2 (end-binding protein), NGL-1 (netrin-G1 ligand), and amphiphysin (proteins involved in synaptic structure). At the synapse, the protein also binds to and interacts with several synaptic structural elements such as PSD-95 (postsynaptic density protein 95).<sup>3</sup>

A large number of different mutations of the CDKL5 gene have been detected in individuals with CDD and are rarely the same from one individual to another. Any mutation that interrupts the production of the CDKL5 protein or interferes with its catalytic function is likely to be pathogenic.<sup>4</sup> Nonsense or protein-truncating changes coded by mutations in the CDKL5 gene are disease-causing, as are missense changes coded by mutations associated in the catalytic domain. Although there could be some relationships between genotype and phenotype of the disease,<sup>5</sup> evidence is limited.<sup>3</sup> In rodent models, genetic manipulations that knock out or reduce CDKL5 protein expression negatively impact behavior, as well as visual and synaptic functions.

Researchers have now used these rodent models to investigate whether existing medications could potentially address some of the molecular pathway abnormalities seen in CDD.<sup>1</sup> Despite some limitations, their findings support small and large molecule therapeutic approaches for CDD.<sup>1,3</sup> In addition, at the PFDD meeting, Dr Tim Benke, of the University of Colorado School of Medicine and Research Director of the Neuroscience Institute at Children's Hospital Colorado, said that evidence from the rodent studies showing impacts on neurological function and behavior "supports the suggested diagnostic criteria for CDD clinical trials: Broadly, inclusion is any alteration of the CDKL5 gene and confirmation that the alteration is pathogenic."

## The clinical manifestations of CDD

In most cases, CDD presents with early onset epilepsy—usually detected within the first few months of life—that is medically refractory. Epilepsy may start as infantile spasms without hypsarrhythmia and evolve into epileptic encephalopathies that contribute to the severe cognitive and behavioral impairments observed in CDD. Later in life, children with CDD may experience many types of seizures or a mixture of seizures (tonic, atonic, clonic, myoclonic clusters, and absence seizures) and a spectrum of severity, duration, and frequency (usually daily, but in some individuals weekly or monthly) that evolves over the course of their lifetime. Consistent with CDD being a developmental encephalopathy, many

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<sup>3</sup> Benke T. CDKL5 Deficiency Disorder (CDD): Overview for PFDD FDA Meeting. Externally Led Patient-Focused Drug Development Meeting on CDKL5 Deficiency Disorder; November 1, 2019; College Park, Maryland.

<sup>4</sup> Hector RD, Kalscheuer VM, Henning F et al. CDKL5 variants. Improving our understanding of a rare neurologic disorder. *Neurol Genet* 2017;3:e200; doi: 10.1212/NXG.0000000000000200.

<sup>5</sup> Mangatt M, Wong K, Anderson B et al. Prevalence and onset of comorbidities in the CDKL5 disorder differ from Rett syndrome. *Mangatt et al. Orphanet Journal of Rare Diseases* (2016) 11:39. *f Rare Diseases* (2016) 11:39 DOI 10.1186/s13023-016-0418-y.

children have a seizure honeymoon at 1 or 2 years of age that may last several months to a year. Epilepsy can, though rarely, improve with age.<sup>3</sup>

Upon clinical evaluation, other debilitating features are discovered in infants and young children with CDD, including hypotonia (very low muscle tone), cortical visual impairment (poor motor planning and challenges with visual tracking affecting reach, the ability to focus and make eye contact), severe and global developmental delays including an inability to communicate, slow or no development of hand use, and hand stereotypies. Other features that may emerge later in life include movement disorders, laughing and screaming spells, teeth gnashing, sleep disturbances including night waking, sleep apnea and ‘all night parties’ (prolonged periods without sleep), irregular breathing, swallow dysfunction (sometimes requiring gastrostomy), severe gastrointestinal acid reflux disease (GERD) and constipation. These features can take a toll on the body’s other organ systems leading to complications such as chronic aspiration pneumonia which can be lethal and scoliosis that is often severe enough to require surgical correction. In addition, the natural history of the disease may be further complicated by the side effects of treatment that may address one symptom at the cost of worsening others and creating new treatment-related comorbidities. Subtle dysmorphic features are another common observation that include a broad/prominent forehead, large deep-set eyes, deep philtrum, anteverted nares, full lips, and tapered fingers and toes.<sup>5</sup>

There is a very wide spectrum of severity in CDD. Intellectual disabilities may be profound and complicated by the challenges processing visual information. Some children never meet or have greatly postponed developmental milestones—some may have difficulty lifting their heads and never sit unaided. Most never walk unaided. Many do not achieve a pincer or a raking grasp (precluding the ability to hold a spoon and feed themselves). Many are unable to express their needs or tell their caregivers what is causing them pain or distress, even via body language, facial expressions, simple sounds or gestures. Speech, if it develops at all, is very limited.<sup>3</sup>

However, some children and young people with CDD, though not many, learn to walk—even run—talk and develop functional hand use.

As children grow older, regression of skills is rare, but does occur in the context of worsening seizures—and once a skill is lost, it can be difficult to regain. In addition, even in less affected ambulatory children, complications downstream from hypotonia, such as scoliosis, may complicate mobility in older children. Later in life, hypotonia may evolve into dystonia with Parkinsonian features.

There are several reports of childhood mortality in children as young as a couple of years old. However, there is no quantitative data of total childhood mortality or life expectancy for CDD due to lack of an ICD-10-CM code (of note, an ICD-10-CM code for CDD will be adopted starting in October 1, 2020, enabling epidemiological research). Some individuals over 40 years of age have been identified. “Topic 1” on page 10 will provide greater detail and context from patient and caregiver experience.

## Treatment overview

Given the complexity of CDD, children and adults with CDD require care from a multidisciplinary team composed of many specialists including not only pediatric neurologists, movement and epilepsy specialists, but ophthalmologists that recognize cortical visual impairment, pulmonologists, gastroenterologists, nutritionists, cardiologists and orthopedists with experience working with cognitively disabled children. Access to both genetic testing and good genetic counselling is critical to



diagnosis. Physical and occupational therapists, therapists for speech, augmentative and alternative communication (AAC) and educational vision services are also required, as are specialists in sleep medicine, behavioral psychology, psychiatry, and developmental pediatrics. Both the child and family need the support of social workers and case managers. Finally, there is a need for care coordination and integration—with an eye on how treatments and complications could interact and affect neuromuscular disorders. Only a small number of centers of excellence have expertise managing care for such patients.

There is no published peer-reviewed guidance for the management of CDD. At present, the only treatments for CDD are symptomatic, beginning with approved anti-epilepsy drugs (AED), the effectiveness and tolerability of which may vary from child to child. Regardless of initial benefit, in most children, seizures eventually return and often become worse. Care providers cycle through the approved drugs, using higher doses and combination therapy, though the benefit offered may come at the expense of slowing mental processing speed, increasing attention and language deficits, decreasing motor tone and control, aggravating mood disorders and creating other behavior or physical problems.

*“As pediatric epileptologists add more and more drugs at higher and higher doses to extinguish seizures, we often extinguish part of the child's personality and cognition in the process,”* said Dr. Orrin Devinsky, Director of the CDD Clinic & Epilepsy Center at New York University's School of Medicine at the meeting.

Other treatments for refractory epilepsy are also used including specialized diets, mainly the ketogenic and Atkin's diets, though these are challenging to administer, neuromodulation through vagus nerve stimulation, and even neurosurgery (corpus callosotomy) though there is little evidence of efficacy.

There are also symptomatic therapies for behavioral disorders, attentional problems, GI disorders like constipation or lack of GI motility, and many other therapies and care from specialists and therapists. In addition, individuals with CDD require a wide range of other devices and equipment, such as mobility equipment (strollers and wheelchairs), orthotics support (back and foot braces), nutritional support/ enteral feeding (including G-tube placement), breathing assistance and suction devices, as well as eye gaze devices and other tools to assist in communication. Some caregivers try to engage their children by enrolling them in aquatherapy, hippotherapy and music therapy.

However, there are no approved targeted therapies that address the cause of CDD, no way to modify disease outcome or to counteract the underlying CDKL5 deficiency and all its downstream effects.

At the time of the EL-PFDD meeting, there were several experimental therapies in development, but these all target epilepsy, or, rather, the clinical trials of them are primarily designed to measure seizure-related outcomes. At the time of the meeting, there was one drug in a pivotal trial, and three additional small molecule trials in Phase 2. Epidiolex (highly purified cannabidiol extract) has also been evaluated in CDD as part of large open-label studies with demonstrated benefit in other severe epilepsies.

While more effective and less toxic epilepsy drugs are needed, there is an unmet need to treat the other aspects of CDD. This will require looking at other treatment outcomes beyond control of epilepsy, such as improvement in cognition, cortical visual and motor function, hypotonia and other CDD related outcomes. Evaluating non-seizure related outcome measures could also be critical to the development of experimental AEDs, if one or two of the experimental AEDs in advanced studies prove to be as effective at seizure control as hoped, reach market, and improve the standard of care, as it may become more difficult to adequately power studies to show whether new drugs reduce seizures. “Topic 2” on page 27 will provide greater detail and context from patient and caregiver experience.

## Meeting overview

There were about 100 people in attendance (92 registered participants who attended the meeting in person (plus some who weren't registered); and 158 others followed the meeting through live webcast. About a dozen members of the FDA came to the meeting to hear directly from affected individuals about the burden of disease with CDD and the available treatments and management approaches—though, given the devastating impact that CDD has on an individual's cognitive development and ability to communicate, caregivers spoke on behalf of their loved one's with CDD. Representatives from FDA included Dr Billy Dunn, Director of the Office of Neuroscience, Center for Drug Evaluation and Research (CDER); Dr Susan McCune, Director of the Office of Pediatric Therapeutics; Dr Anne Rowzee, Associate Director for Policy, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research (CBER); Dr Mike Singer, Medical Officer, Division of Clinical Evaluation and Pharmacology/Toxicology, CBER; Dr Lucas Kempf, Medical Officer, Rare Diseases Program, CDER; Michelle Campbell, Senior Clinical Analyst for Stakeholder Engagement and Clinical Outcomes for the Division of Neurology Products, CDER; Eleanor Dixon-Terry, Regulatory Health Program Manager, Office of Orphan Products Development; Julie Vaillancourt, Rare Disease Liaison, CBER; Karen Jackler, Patient Engagement Lead, CBER, Cynthia Welsh, CDER and others.

Approximately 45 of the people who attended the in-person meeting were parents or caregivers of a child or young person with CDD, and in 10 cases, the child with CDD accompanied them. Another 160 others affected by CDD registered to attend via webcast. In addition, family and friends of individuals with CDD, healthcare providers, clinical experts and a broad cross-section of representatives from the pharmaceutical industry, academia and patient advocacy organizations also attended the meeting.

Opening the meeting, Karen Utley, president and co-founder of the International Foundation for CDKL5 Research—and mother to a 13-year-old daughter with CDD—acknowledged how painful it would be for many parents to talk about the burden of CDD:

*“Each of us parents love and adore our child and we do not see them as a burden... Many of us choose to pursue a positive path and focus on the joy and inspiration that we get from our loved one. [However], it is of utmost importance for us to share the challenges, grief and pain that this disorder causes our families. The only way that we can express the true impact of CDD to the FDA and drug developers is to communicate the raw and ugly side of CDD.”*

FDA's Michelle Campbell described the agency's responsibility to ensure that the benefits of drugs in development for CDD outweigh the risks—and how the meeting would help the agency do that: “This dialogue is extremely valuable because hearing from patients and what you care about helps us figure out the best way to facilitate medical product development, and understand how patients view the benefits and risks of therapies and devices in CDD,” she said.

This was followed by presentations from two clinical experts, Dr. Tim Benke, University of Colorado and Dr. Orrin Devinsky of New York University School of Medicine to provide context on the molecular genetics of CDKL5 deficiency, the clinical manifestations of the disorder, current treatment modalities and the clinical trial pipeline (as described above).

The meeting was divided into two sessions designed to draw out the experience with CDD through testimony, polling and interactive discussion. The first session focused on the burden of disease—asking meeting participants to consider which symptoms or effects of the disease had the greatest impact on their loved one’s lives. The second session explored patient perspectives on current and future treatments and unmet needs in management of CDD.

Each session began with a panel of caregivers—parents and one grandparent—who lent their voices to depict the debilitating impact of CDD upon their loved ones’ lives, describing the health effects on many different bodily systems that vary from one individual to another. They also shared the toll taking care of a child or young person can exact on caregivers and other family members.

After testimonies from members from each panel, a series of polling questions were posed to the participants in person at the meeting and those watching via a live-streaming webcast to obtain an understanding of the full impact of the disorder on the community. Participation in the poll was voluntary and while 77 individuals registered on the polling site, on average, about 66% provided responses to the questions. (Note, the results were used as a discussion aid and should not be considered scientific data.) Responses were used to facilitate an interactive discussion providing other caregivers and family members in attendance an opportunity to “pull back the curtain to share their difficulties and heartbreak,” in the words of discussion moderator James Valentine of Hyman, Phelps & McNamara. (Valentine helped start the PFDD program when he worked at FDA. He also helped to plan the meeting.)

After the facilitated discussion, Valentine’s colleague, Larry Bauer, Senior Regulatory Drug Expert at Hyman, Phelps & McNamara, who was also recently with the Rare Disease Program within CDER at FDA, provided a synopsis of the key messages from the meeting for regulators and industry. Finally, Majid Jafar, founder of the Loulou Foundation, and father of a 5-year-old girl with CDD, closed the meeting reiterating what he believed to be some of the key messages the community wanted FDA and drug developers to hear (see Conclusion on page 61)

To supplement the feedback from the meeting, a questionnaire was also sent out, particularly to gather caregivers’ perspectives on how they would balance the benefits versus risks of current and potential treatment options. Thirty-six individuals completed the survey, including some who were physically unable to attend the meeting. Highlights of the survey are summarized in section III on page 45. (Complete responses are shared at [www.cdkl5.com/pfdd](http://www.cdkl5.com/pfdd).) These responses also helped inform the development of the Benefit-Risk Framework for CDD on page 59).

## Report overview and key themes

This report summarizes the input provided by caregivers during the meeting. It also includes a summary of comments pertaining to benefit-risk submitted to the post-meeting survey.

To the extent possible, the terms used in this report to describe specific symptoms and treatment experiences reflect the words used by in-person participants and language used in submitted survey responses. There may be symptoms, impacts, treatments, or other aspects of CDD that are not included in the document. This report is based upon structure of the meeting, followed by a description of the findings of the post-meeting questionnaire, the benefit-risk framework, and the meeting conclusion.

## Topic 1: Key messages on the burden of disease in CDD

The first meeting session focused on the burden of disease in CDD. The feedback from the panelist testimonies, polling and facilitated discussions as well as from the post-meeting questionnaire portrayed a debilitating, developmental disorder with refractory epilepsy that can prevent neurocognitive development, thwart the ability to communicate verbally and non-verbally, profoundly impair gross and fine motor function, cortical visual function, and autonomic function, and create a multitude of downstream health conditions that cause tremendous suffering and can ultimately be life-limiting.

### *A few key themes emerged:*

Although seizures are generally a hallmark of CDD, the symptom first recognized and leading to diagnosis and almost always refractory to treatment, the type of seizure, frequency and severity can vary substantially by individual and evolve over the course of life. Additionally, caregivers prioritized global developmental delay—with its impact on a wide variety of bodily systems—as having the greatest impact on quality of life—severely stunting neurocognitive development in most and hindering meaningful engagement between the child and their families as well as their environment. The severity of the developmental challenges and functional impairments varies from individual to individual; however, there is a pattern in how the disorder manifests:

- Seizures usually present in infancy, within the first few months of life, though there seems to be a handful of outliers where the first observed seizure occurs months or even years later. The refractory nature of the epilepsy is often well established by the time of diagnosis.
- By this time, the global developmental delay is also unmistakable. Infants have difficulty making eye contact; hands do not grip; some babies have difficulty nursing. Many never reach their basic developmental milestones even into adolescence. Others develop skills only to lose them after severe periods of uncontrollable epilepsy that wipe them from memory.
- Around 1 year of age, children may have a honeymoon period of several months without seizures. During this period, and later while seizure activity may be curtailed for a period by AEDs, a more sustained period of development may occur. Children may begin reaching milestones and sometimes retain them when the honeymoon is ended. Cortical visual control may improve somewhat. Some children learn to hold spoons. Some children even learn to walk and talk a bit.
- When the seizures return, the pattern evolves in a variety of ways that may in part depend upon responsiveness to treatment. Some develop recurrent tonic seizures; others, clusters of seizures; some may have violent seizures lasting for 10-20 minutes, while a few have only odd absence seizures.
- As children grow, autonomic dysfunction contributes to slow motility leading to constipation, and gastroesophageal reflux disease (GERD) that can cause extreme distress and discomfort, and, some caregivers believe, trigger seizure activity. Caregivers stress about management of their child's bowel functions and the need to change diapers can present a challenge to going out into public with them as their bodies grow.
- The child may develop behavior disturbances during this time, with uncontrollable screaming fits, teeth grinding, and self-injury that may be due to anxiety or some distress the child cannot communicate. These behaviors can traumatize siblings and make it difficult to take the child out in social settings when people are not always accepting. Sleep disturbances that can last for days on end, called all-night parties by some, also present challenges for caregivers who must work, or who feel the need to provide supervision around the clock to keep the child from hurting themselves or from choking during a seizure.
- The inability of a child to communicate, whether verbally or non-verbally was perhaps the most devastating to caregivers. One said that it was “indescribably sickening” not being able to help their

child because they must guess whether their crying stems from pain, hunger, or discomfort. Others said grieved because they were unable to engage with their child, unable to see their personality, knowing their child was trapped in her or his body and unable to express themselves.

- Hypotonia remains an important problem as children age leading to life-threatening complications such as difficulty to swallow, inability to eat, and challenges with aspiration that could lead to pneumonia and trips to the ER or worse. Older children and adolescents may develop bone problems associated with the low tone, fractures, hip dislocation and scoliosis.
- While some children learn to walk, even run, speak words and even sentences, as children grow into adolescence and young adulthood, some caregivers at the meeting described the pain seeing their child lose these cherished abilities.
- Finally, it should be noted that the male/female sex distribution among the respondents seemed to reflect what would be predicted by X-linked disorder—with boys having particularly severe life-threatening forms of the disorder. There were no testimonies from caregivers of adolescent boys at the meeting. The oldest individual with CDD represented in the meeting or post-meeting questionnaire was a 35-year-old woman.

## Topic 2: Key messages regarding perspectives on the treatment options in CDD

The second session of the meeting focused on caregiver perspectives on current and future treatment options. Several key themes emerged from testimony, comments and post-meeting questionnaire:

- For seizures, there are a multitude of AEDs—though some children had cycled through most of them before they diagnosed. At best, the drugs work for a short while and are only partially effective. Most do not work. Some AEDs aggravate seizure activity dramatically in certain patients, even, in rare cases causing status epilepticus. The process of titrating up, monitoring side effects, and weaning off the medications when they stop working is exhausting to child and caregiver alike. In addition, the AEDs have little—if any effect—on the global developmental outcomes that matter most to caregivers. Though keeping seizures under control may prevent disruptions that make neurocognitive issues worse, they often sedate, confuse or dull the personality of the patient.
- Some caregivers had positive things to say about the benefits of ketogenic and/or modified Atkins diet (slight seizure reduction and improved cognition), but it is very difficult to prepare. Caregivers were uncertain whether it was still helping but afraid to take the child off the diet.
- Caregivers often give up their careers in order to provide their children a wide range of treatment and multidisciplinary care to manage the symptoms of CDD, and while these may deliver small changes, sustaining the individual with CDD by treating their constipation, help them to sit up and be mobile, communicate a little, and suction their secretions, they do not treat the condition.
- There are no therapies that treat the symptoms that matter most to the CDD community: to treat the neurocognitive and functional impairments, the developmental delay, or significantly improve language abilities or social communication, the lack of gross and fine motor function—by treating the underlying cause of the disease. Caregivers stressed that addressing the CDKL5 deficiency may be the only way to achieve lasting effects on seizures, address the hypotonia and other downstream symptoms that create anxiety and discomfort and shorten the lives of people with CDD.

## Feedback on benefit-risk in post-meeting questionnaire

Responses to the post-meeting questionnaire about the symptoms that mattered most, and the benefits and limitations of treatment, were largely consistent with what was described at the EL-PFDD meeting. The demographics were similar, perhaps slightly older, with a slightly larger representation of individuals

who caregivers described happy and in good health. Thematic analysis of the responses led to several observations:

- Manageable routine side effects may be acceptable to most caregivers as long as there is no decreased quality of life or increased suffering, and as long as they do not outweigh the benefits for treatment. There is, however, small subset of caregivers who are not willing to take risks in their children with relatively stable health.
- Most caregivers will apply the same criteria to trying potential new treatments as they apply when choosing between AEDs and other therapeutic options with sometimes significant side effects.
- Pain or suffering is a particularly important factor to consider when a child cannot communicate and should be monitored carefully in clinical trials of CDD.
- Caregivers of children who are very ill or whose life is in jeopardy due to CDD will accept a high level of risk for a global treatment—as a treatment for the underlying cause of the disease may be the only way to keep their child alive.
- Most CDD caregivers would accept some risk of death to access a partially effective treatment for the global symptoms, though some would prefer to wait until a product's safety is established.
- A third of the respondents have already been in clinical trials, most would continue doing so again. Among those who have not, there is again the subset that is averse to risk in their children. The remainder would consider entering a clinical trial, depending upon the criteria, their child's present needs and what is known about the potential effectiveness and safety of the treatment.
- The most important factors that people listed as affecting their decision to enter a trial was how the treatment might improve the child's health, concern about the risks of serious side effects (e.g., cardiac or liver issues), the reputation of the study site principal investigator (doctor) and nearness of the study site / travel required.

## Benefit-Risk Framework

The patient input generated through this EL-PFDD meeting and post-meeting questionnaire is submitted to strengthen FDA's understanding of the burden of CDD on patients and their perspective on the treatments currently used to manage CDD and its symptoms. It is our hope that FDA staff will carefully consider this input as it fulfills its role in the drug development process, including when advising sponsors on their drug development programs and when assessing products under review for marketing approval. For example, the Benefit-Risk Framework on CDD (on page 59) shows how this input may directly support the FDA's benefit-risk assessments for products under review. This input may also be of value to the drug development process more broadly. Specifically, it may be particularly useful to drug developers as they explore potential areas of unmet need for CDD patients, for example with regards to managing psychiatric symptoms or increasing overall symptom control. It could also point to the potential need for development and qualification of new outcome measures in clinical trials.

## Appendices

The appendices include the meeting agenda, details on participants, polling questions and results, and links to additional meeting materials.

Additional information on the meeting has been posted online at [www.cdkl5.com/pfdd](http://www.cdkl5.com/pfdd), including the [webcast](#) recording.

## Topic 1: Most significant symptoms and their impact on daily life

The meeting's first session focused on the symptoms of CDD and the burden of the disease upon the daily lives of individuals with CDD, their caregivers and families. Just before calling the first panel of caregivers to the stage, however, some live-polling questions were asked to capture who was being represented during the meeting.

Consistent with the demographics as identified in the natural history data, over four out of five of the polling respondents' children were female (83%) and less than one out of five were male (17%). Seizures began extremely early: 59% of respondents said that they started during the first month of life, and 31% between 1 and 3 months of age and only 7% between the age of 6 months and 1 year (note, 3-6 months of age was accidentally omitted as an option). Only one respondent said that the first seizure occurred later in their child, after 2 years of age.

However, diagnoses often came months or years after the seizures began. Slightly over a third of the children were diagnosed before 6 months of age, a third between 6 months and 2 years of age—but almost a third only received the proper diagnosis after the child was more than 2 years old (note, these would include the individuals born before gene screening was available). At the time of the meeting, all polling participants' children were over the age of 1 year: 16% were 1-2 years old, 24% 3-5 years old, 24% 6-10 years old, 29% 11-18 years old, and 7% over 19 years old.

Although her own daughter is now 13 years of age, the trauma of the CDD diagnosis was still fresh in the memory of IFCR's founder Karen Utley, who provided the meeting's first glimpse into the lives of those affected by CDD that had been offered during the introduction:

*“When your child is diagnosed with a disorder such as CDD, your world changes. I [felt] like I was drowning, literally, in a body of water with waves crashing over my head and taking my breath away.”*

Utley described an experience common among many of the parents of children diagnosed with CDD—terrifying as the seizures may be, the global developmental delay soon observed in the child may be even more devastating:

*“In the beginning, all I wanted to do was stop the seizures. However, as she grew, it became crystal clear that this disorder is not simply an epilepsy. Accepting the reality of the situation and understanding that short of a treatment and a cure, your child will not develop into an independent adult, is a crushing blow.”*

### Panel testimony

The panelists, representing children ranging in age from 17 months to 17 years old, reported similar experiences.

- *“We were given a grim prognosis. Not only will she likely never walk, talk, feed herself or achieve seizure freedom, but her life itself may be at risk,”* said the first panelist, mother to a 17-month-old girl who started having seizures before she was five-weeks old. Initially, her family was relieved to



see her meet some developmental milestones, only to be followed by a period of regression or loss, the most recent of which was precipitated by a life-threatening medical crisis due to her medical care. (see thematic discussion). This danger became the caregiver's overriding concern: *"Our family focuses a lot on skill acquisition... however, our priorities shifted considerably, reminded that life preservation itself cannot be taken for granted in CDD."* The broad range of symptoms and health conditions also make it difficult to prioritize care: *"We cannot focus on developing her vision when she's screaming in pain from constipation. We cannot work on eating solids when she will not drink water. We cannot read or play with her when she's disconnected from the world around her. It seems that instead of moving in a forward trajectory, we travel in circles. We are not sure what will happen tomorrow, which makes it very hard to plan or develop expectations."*

- *"Three weeks after a typical healthy birth, our youngest daughter suffered through 11 seizures in one day,"* said the second panelist. Receiving her child's CDD diagnosis, she learned her daughter was *"at risk of every type of seizure."* Over the next few months, although the frequency decreased, the duration increased until she had one long seizure a day. At this time, the lack of normal development *"became glaring."* When she was 3 years old, she started having spells lasting for several months, with fits of crying and *"uncontrollable, inconsolable screaming, and whole-body thrashing"* but the child could not communicate the source of her agitation. A couple of years later, when she *"stopped eating and would barely drink,"* a trip to the ER revealed the cause—severe constipation. After she was treated with laxatives the family *"could once again find some reprieve."* The burden of caregiving had had a terrible impact upon the caregiver's own health leading to heart disease. This has made her more concerned about the effects of *"stress [her daughter's] little body faces every day as a result of her seizures, GI complications, lack of sleep, and sensory issues."* While she wonders whether her daughter, now 7 years old, will *"ever walk or even take one step. Will we ever hear her little voice? Will she ever engage with us?"* she said, *"the most pressing question is, how long will her body endure the torment of CDKL5?"*
- The third panelist was mother to a 3-year-old boy with CDD whose first seizure *"was the same day that I took his one-month baby photo. I was holding him sleeping outside on our deck when suddenly all four of his limbs were jerking. We learned of his CDKL5 diagnosis at six months,"* she said. *"That first year of his life was emotional."* In addition to his *"daily seizures,"* his hypotonia prevented him from meeting any milestones. While, with therapy, he did make some progress, most of the abilities gained were lost after he became ill with severe ear and respiratory infections. Then, *"his seizures became completely out of control"* increasing in number and intensity, leading to exhaustion and loss of the ability to be fed by mouth. Respiratory challenges, inability to clear secretions, have now resulted in two hospital admissions, and she is worried that he might choke on his vomit during a seizure. *"I have no doubt now about [CDD's] ability to be a life-limiting diagnosis,"* she said.
- The fourth panelist's 10-year-old daughter started having multiple seizures several times a day when she was 5 weeks old. Forceful and refractory to treatment, the seizures left the 8-week-old infant exhausted and her body *"completely limp."* She was one of the children with seizure honeymoons *"that could last several months,"* and during that time, she learned to *"sit independently, transferring object from one hand to another, and sipping from a straw."* However, at the age of 4 years, *"after a month-long hospital stay due to status epilepticus,"* she lost all those skills. *"Uncontrolled seizures bring on more debilitating CDD symptoms,"* such as her daughter's hypotonia, *"and affect the gained skills."* Now, she believes her daughter's hypotonia are causing bone and spine weakness, as well as trouble clearing secretions from the back of her throat. Even more disturbing to the caregiver, is that her daughter has had to endure painful injuries because she



had no way to communicate the cause of her distress. Totally dependent upon her parents, as she grows older, the caregiver expects her daughter will increasingly need medical equipment and other accommodations—as well as *“special needs, trusts, and wills”* for her future care, she said, *“so we know that she will always be taken care of, especially if we’re no longer here.”*

- Although his daughter *“began having seizures when she was 2-weeks old,”* and clearly *“wasn’t meeting milestones”* as she grew older, the final panelists’ daughter did not receive her CDD diagnosis until her 11th birthday. Now she is 17 years old, and *“in addition to the ever-present seizures, the primary issues [she] suffers from are limited mobility, cognitive and communications impairment, and gastrointestinal problems.”* She has had a G-tube surgically implanted because she was aspirating fluids when she swallowed, and an appendicostomy to deliver medications to manage her constipation and diarrhea. Meanwhile, though better able to engage than some children with CDD, she is still profoundly developmentally delayed. For a while, she could speak with *“a vocabulary of about 10 or so words,”* but she has now lost that ability. In addition, she could once even run. Recently, however, she has become unsure of her steps and requires a stroller. *“Can [she] remember running? Can she remember racing through the mall? Part of me hopes she can’t. Still, I think in her dreams, she runs,”* her father said.

The briefs above offer a snapshot into each testimony. Many of the most powerful insights are included in the thematic analysis below (which also includes input from the second panel and topic discussion).

Several key themes emerged in the panelist’s testimonies. All the caregivers observed seizures very early in their child’s life (when they were 2-5 weeks old), occurring multiple times each day (as many as 25 per day) that have evolved in pattern and duration (down to one as long as 15-20 minutes, and an episode of even life-threatening status epilepticus [30 minutes or longer]) either as a result of natural history or treatment. Each of the children suffered profound global developmental delay varying slightly in severity—most never met development milestones due to the direct neurocognitive effects of CDD, and damage caused by the seizures to the brain and body—including hypotonia affecting motor and physical function). While children have slowly gained skills, those abilities could be lost suddenly, due to the seizures, other disease-related complications that lead to intercurrent illnesses (such as aspiration pneumonia), and sometimes the effects of treatment. Moreover, caregivers were painfully aware that complications and adverse events could abruptly end their child’s life.

Further complicating caregiving, the inability to communicate, even non-verbally—some could not engage at all—could make it impossible for the caregiver to ascertain the cause of crying or screaming or detect the presence of injuries or potentially life-threatening complications, forcing the child to endure extreme discomfort and pain for months at a time. This could be the source of behavior that is extremely disruptive to family life, frightening to other children, and emotionally devastating for caregivers who question their self-worth as parents.

Other complications were also common (possibly the consequence of hypotonia and impaired autonomic function), as children developed problems with cough, swallowing and clearing secretions from their throats, and gastrointestinal problems—particularly constipation. Similarly, weakened bones, increasing the risk of fractures in the context of violent seizures, and spine curvature could be a result of hypotonia and lack of core strength. Some of the children are too weak to sit unaided. Even the one child who could once run has grown too unsteady on her feet to walk unaided.

The panelists also described how all-consuming caring for a child with CDD can be and the many ways in which their child was completely dependent on their care. This profound burden of care places tremendous physical, emotional, psychosocial and financial demands on caregivers.

## Perspectives on symptoms that matter most to patients and their caregivers

During polling and the facilitated discussion, participants expanded on themes raised by the panelists. Perhaps first among these was how extensively CDD affects so many aspects of development, functional domains and organ systems—and how many of these deficits are interrelated. As Utley said in her intro: *“This disorder impacts our kids greatly and globally...Although CDD is certainly neurological in its origin, the impact creates symptoms in many body systems.”*

Before the discussion, there were three polling questions posed on symptoms and disease complications and the burden of disease. Note, the first of these revealed the breadth of the disease impacts experienced by individuals with CDD. Participants were asked to select all out of a choice of 12 symptoms and health effects (including ‘other’) their child was currently experiencing. The following selections were made by 49 respondents:

- 100% reported their child was affected by global developmental delay.
- 98% indicated that their child’s speech was limited or absent.
- 96% of their children with CDD experience epilepsy/seizures.
- 94% have difficulty walking.
- 90% have limited hand control.
- 88% have some form of visual impairment.
- 88% experience sleep problems.
- 82% suffer from some form of gastrointestinal and feeding problem.
- Almost 80% have behavioral disturbances (such as hypersensitivity, agitation, irritability, stereotypies, bruxism, or self-injury).
- 57% had respiratory problems (e.g., aspiration challenges, irregular breathing, etc.).
- 40% have developed scoliosis (curvature of the spine)—a complication observed among older children with CDD.
- Almost 35% indicated their child was experiencing other complications that were not on the list.

When forced to choose the top three symptoms out of the same list that were most burdensome for their child, however, marked distinctions emerged. The symptoms below are ranked in the order based upon the percentages of responses to this question. However, although there were commonalities when asked to elaborate on their family stories each child was unique with their own constellation of symptoms. In addition, for many, what was most burdensome had evolved during the child’s life. Finally, the discussion also demonstrated that many of the symptoms could not be entirely divorced from one another. Caregivers linked symptoms together in the same breath—this was particularly true of global developmental delay, which was defined somewhat differently from caregiver to caregiver. [Full polling results can be found in Appendix 2].

## A. Global developmental delay

*“[Her] cortical visual impairment, her fine and gross motor skills deficits, and her profound intellectual disability were the things we thought had the biggest impact on her quality of life.”*

Of all the consequences of CDD, it was global developmental delay that caregivers felt most impacted their child’s life—selected by approximately 79% as a top three most burdensome symptom. In part, this may have been because global developmental delay underlies many of the symptoms in CDD, including not only cognitive disabilities but motor and physical impairment.

*“Her motor deficits means she cannot enjoy the textures and sounds of objects around her because she cannot reach them if they are outside of her immediate vicinity,”* one panelist said about her infant daughter. *“More importantly, her intellectual disability makes it hard for her to help us understand her needs and to navigate her world by learning and applying knowledge. For instance, if a toy drops from her hand, it may as well have fallen off the edge of the world. She does not appear to miss it once it has gone or reach for it to get it back.”*

Other caregivers saw global developmental delay as the barrier preventing engagement and communication with their child: *“She wasn’t smiling... She would not engage,”* said one.

The motor and physical aspects of global developmental delay in CDD were at least partly attributed to hypotonia: *“His low muscle tone meant that he struggled significantly with the most basic of gross motor tasks. He couldn’t lift his head. He couldn’t reach. He needed his bottles to be thickened in order to drink them safely. As he grew, [he] never officially met any of his milestones,”* said one panelist.

Global developmental delay was apparent during infancy: *“By the age of 6 months, it was already clear she wasn’t meeting milestones,”* one caregiver said of his daughter.

Consequently, families and therapists *“focus... a lot on skill acquisition.”* But a few caregivers described heartbreak when their child’s skills—and cognizance—were lost after health crises... in some cases, serious infections, in others, severe seizures (including status epilepticus): *“She continued to develop, rolling, holding her head up in tummy time, cooing and tracking and reaching for certain objects. We were encouraged until about six months in, when progress came to a halt. [She] spent weeks in a constant state of lethargy and irritability, not utilizing her skills or interacting with us,”* said one mother.

*“No longer can he prop sit or keep his head up, even with trunk support. Right now, he can’t even lift his head up off his chest. We struggle with how to position him properly so he can engage with our family or work on his vision or other therapies,”* the mother of the 3-year-old boy with CDD said.

*“She would have periods of seizure freedom that could last several months; during those times, she was gaining skills, albeit very slowly,”* but these were lost when her seizures returned. *“Once a skill is lost, it is very difficult to gain back,”* said panelist, who is mother of the 10-year-old girl.

Although most caregiver’s spoke about global development delay in the context of early childhood and failure to meet milestones, it persists for children and adults with CDD, and is painful to discuss. However, some mentioned that persistent communicative and physical impairments are a source of frustration to adolescent children who would like to engage but cannot.

*“We chose global developmental delay,” said the mother of a 12-year-old girl during the facilitated discussion. “For our daughter, seeing other children, her cousins, playing, and not being able to interact with them is probably, it’s for us, one of the most difficult things, and, I think, for her as well.”*

Others with more severe cognitive impairment face or grow into an adulthood fixed in infancy.

*“At 17, [she] thinks and communicates at the level of a one-year-old,” said one panelist.*

## **B. Epilepsy/seizures**

*“While most of our children have seizures, they continue to change over the years. [My daughter is] 11 now and we’ve seen every kind of seizure under the sun.”*

Epilepsy, part of a proposed diagnostic criteria for CDD, was chosen by 63% of the respondents as one of the top three most burdensome symptoms and was by far the most discussed—possibly because it is the first unmistakable sign something is gravely amiss: *“the first symptoms we noticed were seizures.”*

*“Seizures at 19 days old,” said the founder of the Loulou Foundation of his daughter’s first seizures. The timing of seizure onset ranged between 2 weeks and six weeks, with one outlier whose daughter’s first seizure occurred at the age of 7 months. In some cases, the first indications were subtle or hard to distinguish from a startle reflex. “I first noticed [her] making movements, like the moro reflex, but sensed and said something was very wrong,” said a caregiver on the first panel. A caregiver on the second panel described “strong startle episodes which eventually proved to be infantile spasm seizures.”*

In others, the initial intensity was far greater, *“[Her] seizure activity started as three to four one-minute long episodes each day, with most occurring during the day,”* one caregiver said, but the pattern changed over time: *“By 7 months old, her seizures became a little less frequent, but longer in duration, having a couple more per day but lasting 10 to 13 minutes each, often in the middle of the night. By 8-months old, [she] was having one long seizure every day lasting 15 to 20 minutes. They seemed to be at their worst when [she] fell asleep, and she would wake up screaming as if in excruciating pain.”*

Other caregivers also described an evolution in type, frequency, and severity of seizures over time.

*“Not a day goes by wherein... my intractable epilepsy... is not an issue. And as I grow, seizures wax and wane in both kind and severity,”* said a caregiver on the second panel on behalf of his granddaughter.

*“[Six months ago], his seizures became completely out of control. He started having tonic seizures that went into clusters of spasms so intense and prolonged that he would sleep for hours after each one, and he was averaging nine a day. For weeks, it seems all he did was seize and sleep,”* said one mother. At the time of the meeting, he was averaging *“25 seizures a day, and about five of them happen overnight.”*

*“His seizures have increased in types over time,”* said the mother of another boy. *“Currently the intensity of the physical movements, the rigidity of his body, and the length of seizures from two minutes to now clusters of seizures lasting about 45 seconds, have decreased with treatment. But the frequency has only slightly decreased by two to four per day.”*

As the previous case illustrates, treatment plays some part in changing the pattern of epilepsy—though effects wane with time. *“Slowly over the course of two years, the seizures crept back in, getting longer and more intense until she ended up hospitalized,”* said another caregiver, who added that on some medications, *“her seizures skyrocket[ed].”*

A change in AEDs or the ketogenic diet as well as severe infections and constipation were among several triggers for worsening seizures—even to the point of status epilepticus in some. Others mentioned observing a different seizure pattern emerging in their daughters as they enter puberty:

*“In the past three years, as she nears puberty, her seizures have evolved into a cycle with two weeks of intense seizure activity followed by a 30-day break,”* said one panelist.

*“Our daughter’s seizures... come in clusters,”* said a father during the facilitated discussion. *“We will go three, four weeks without really seeing any seizures whatsoever, and then we call it her bad week. Usually it’s connected to her female cycle and she has two, three, four, five days where she’s not eating; she’s not drinking; she’s just having clusters of seizures.”*

Another nearly universal aspect was how refractory the seizures are to treatment. *“Her seizures continued uncontrolled,”* said one caregiver, while another, whose daughter had failed more than twenty drugs before diagnosis at age 4 years, said, *“When she was diagnosed, we knew that obviously, intractable epilepsy was the main symptom, and that we were probably never going to get control.”*

Others mentioned other impacts of the seizures: *“We admitted her back to the hospital because she had no quality of life, sleeping 22 out of 24 hours a day. This brought on other debilitating symptoms. Lack of seizure control is devastating. It negates any small gains she may have had.”*

*“There is a variance in his symptoms based on seizure activity. During times of increased seizures, he has a harder time participating in therapies, school and social, home life,”* said the mother of one young boy with CDD, while his older brother attending the meeting added, *“I get anxious that he could have a very big seizure, and he could end up in the hospital for a very long time.”*

*“At the clinical level, I often feel that I’m seen as just a seizure nuisance,”* said the grandfather on behalf of his granddaughter, suggesting the preoccupation with seizures leads to other needs being neglected.

### C. Gastrointestinal and feeding problems

*“It reached the point that [she] stopped eating and would barely drink. Upon reviewing a whole-body bone scan... they saw a small glimpse of her stomach. It was significantly impacted. After numerous stool softeners, laxatives, and enemas, [she] finally got some relief. Thirteen diapers later, the screaming had stopped.”*

Nearly half (48%) of polling respondents selected GI and feeding challenges as one of the top three most impactful symptoms in their loved one’s life. Comments ranged from *“difficulty nursing”* and feeding challenges, to slow motility, severe constipation, vomiting, dysphagia and gastroesophageal acid reflux disease (GERD).

*“[She] stopped eating. All I want is for her to eat or at least drink a little water,”* one caregiver of an infant girl said. *“The weekly blood draws she has to endure revealed that this refusal led to acidosis, hypoglycemia, and hyperkeratosis.”*

Feeding challenges appear to be a consequence of neuromuscular and autonomic dysfunction: *“He was unable to suck from his bottle. He wasn't able to drink from any cups. Suddenly, his feeding challenges became a lot more difficult as I struggled to get enough fluids into him by spoon-feeding his purees. Alertness was so compromised that he wasn't strong enough to eat by mouth, and over time, he lost that skill too. Right now, he is 100% fed via G-tube,”* said the caregiver of the 3-year-old boy.

Autonomic dysfunction contributes to slow motility leading to constipation causing extreme distress and discomfort: *“Decreased gastrointestinal motility has manifested mostly as constipation and severe abdominal cramping,”* said one caregiver on the second panel, while the father of a 17-year-old daughter on the first panel said, *“The other GI issue is constipation. Most of [her] life has been a roller coaster swinging between constipation and diarrhea. [She] has landed in the hospital with acute constipation several times. And anyone who's ever played Oregon Trail knows the dangers of diarrhea.”* During the facilitated discussion, his wife spoke about the challenges managing this on a day-to-day basis:

*“The least glamorous topic we all deal with every day, from the moment we wake up, is poop. Gastrointestinal and feeding problems are our daily struggle. We have been on our journey with [her] for 17 years. Literally, our daily discussion is poop. How was it? Was it enough? I would give \$1 million to have a regular movement every day for our daughter. It's a daily constant.”*

Constipation impacts her other symptoms: *“What we we've known but struggled through, if we don't have a healthy gut— and our children do not pass stool regularly, constipation is an extreme problem—that does contribute to epilepsy and the amount of seizures she has. It snowballs into a horrible storm.”*

A caregiver on the second panel offered a similar insight: *“When she was seven years old, any significant degree of constipation was clearly linked to an increase in her seizure activity.”*

Later in life, dysphagia, GERD and vomiting may lead to health emergencies. *“Overnight vomiting... My husband and I just can't handle well. Not only does [my son] have a G-tube placed, but he has ulcers, eosinophilic esophagitis. He has severe GERD. He has slow motility. He has to have an annual upper GI and lower GI scope, and they take a biopsy of his tissue to check for eosinophils count... The GERD may trigger vomiting. It can be as frequent as a couple times a week,”* one mother said during the discussion.

#### **D. Limited or absent speech**

*“One of the most unbearable aspects of CDD is knowing your child is desperately trying to tell you something but not truly being able [to] hear what it is they are trying to say.”*

Limited or absent speech was selected as one of the top three most burdensome symptoms by 37% of respondents—though concerns also extend to the inability to use eye contact and gestures to communicate.

Some of the parents expressed a desire to simply connect with their child: *“[My daughter] is very trapped. She's, I think, more cognitively aware than she's able to express,”* one mother said. *“She's sitting right here beside me, but she cannot tell me what is on her mind,”* said another.



The father fortunate enough to have a daughter who learned how to speak several words recounted how he had *"only heard her say 'dad' twice. Imagine going 17 years and hearing your child say 'dad' twice. 'Daddy,' not even once."*

*"The speech, to hear, to have a conversation and to help my child in pain, where we can't discover what's wrong, and I can't help... You're completely helpless as a parent. That is probably the most heartbreaking for me,"* said another caregiver during the discussion. *"We know that we have a child trapped in that brain. When I can look in her eyes, and she can soulfully look to me, and I know that she can understand some things—and actually mischievously. That brings me joy. If she does something simple like hitting something and laughing, and if I can tell her, 'No, that's not nice,' and she can smile a little bit, I know she understands me, but she can't communicate that."*

But the inability to explain the source of distress weighs heavily on caregiver's minds: *"Some nights, it's that she's screaming and crying, and cannot communicate what's wrong,"* said Utley during her intro. Moreover, the inability to tell a parent when something is hurting can result in long-term health consequences: *"She has a chronically dislocated left hip because she can't speak to me... she can't speak to me,"* said one mother of a 23-year-old young woman with CDD later in the meeting.

## E. Visual impairment

*"Her inability to see means that she's not motivated to reach or to move towards a goal. She does not make eye contact or interact visually with the world around her, which makes it hard for her to connect socially."*

Although chosen by 17% as one of the top three most impactful symptoms, cortical-visual impairment is closely linked with global developmental delay and communication. It is essentially a neurological rather than ocular issue, but while delays in processing and motor planning make it difficult to track objects or make eye contact, visual impairment might also contribute to learning delay and problems engaging. With a spectrum of impairment, it is difficult for a caregiver to know exactly what or how the child sees.

*"There was no visual tracking of objects. Our beautiful daughter would not even look at us as we held her,"* said one caregiver. *"She was not visually tracking objects and was light gazing,"* said another during the discussion.

While some children make progress with age, therapy or practice, visual activities clearly take effort on the part of their child. The effort that it takes to focus could be tiring, and in turn, focusing or looking at objects becomes more difficult to do when the child was tired—hindering efforts at communication.

*"Even though we're doing all these therapies, whether it's eye gaze or visual intervention, we don't know how much she's processing. We don't know if she's really selecting things [or] it's just random. We're assuming and we're hoping that she's selecting, 'Mommy, I want to read a book,'"* said one young mother. *"The visual impairment also impacts the hand use majorly. You are just not sure whether it's intentional or not. Whatever communication devices you need, there's that visual part holding you back. Eye contact is a major thing. I just want her to look at me and say 'yes,' 'no,' just with her eyes."*

## F. Behavioral disturbances (e.g. hypersensitivity, agitation, irritability, stereotypies, bruxism, and self-injury)

*“When she was younger, people were more tolerant of some of the behaviors that she has developed over the years... The teeth grinding—there’s many different behaviors that can be very distracting, especially in public. Even at my local hospital, I have had go-arounds with nurses—she’ll bang her head on walls and, if I’m the only caretaker in there, I’m not always in control of some of the things she’s doing.”*

Behavioral disturbances were also selected by 17% of the respondents as being among the top three most burdensome symptoms that could lead to isolation of the child, caregiver and family; (it was cited as causing the reluctance of some to go out in public). It also created stressful situations for the entire family at home, worries that the child might injure themselves, and making it difficult to share family time.

When one toddler with CDD was having screaming spells that lasted several months *“our other children endured many family dinners with sounds of their sister screaming in the background, and many, many sleepless nights. We would have to remove her from the room just to try and have a conversation. As a parent, this was heartbreaking,”* her mother said.

In some cases, the behavior was due to distress the child can’t communicate or simply being tired, *“He loses stamina and he becomes very agitated,”* said one mother. In other cases, it was quite the opposite: *“A lot of the sleep problems that we have are related to hyperactivity: She can’t switch off! We kind of know, at 5:00 in the afternoon, if she’s kicking her legs and thrashing around and laughing like somebody told her a really unfunny joke, that we’re in for a rough night.”*

## G. Limited hand control

*“She would not even grasp her toys.”*

Linked with global developmental delays, about 12% of polling respondents chose the lack of *“purposeful hand use,”* as one of the three most impactful symptoms. *“I see that she has intention to answer me, to move her hand on the choice [switch] but sometimes she has a very hard time because of her hypotonia,”* one mother said. Lack of *“hand coordination or purposeful use of her hands prevents her from telling me what her needs are,”* said one caregiver.

Others focused on the inability to hold objects, such as straws, cups, and spoons. *“Nor can she hold [objects] unless they have very specific shapes and sizes,”* said one panelist.

## H. Difficulty walking

*“[Her] impaired mobility limits more than just trips to the mall. Her bulky stroller, really a type of wheelchair, makes it a challenge to take her into crowded spaces.”*

For many caregivers to children who never reach even early developmental milestones, difficulty walking was not among the top three most impactful symptoms (it was selected by only 12% of polling respondents). Most children with CDD never gain the ability to walk. Even so, its absence was still noted by the Jafar (founder of Loulou Foundation), whose daughter was 5 years old at the time of the meeting: *“Our story is very similar... Still no speech or purposeful hand use or walking.”*



For others who do learn to walk and run, nothing is guaranteed (see next polling question).

## I. Respiratory problems (e.g., aspiration, irregular breathing, etc.)

*“Sometimes, my little brother stops breathing. I’m worried that he will choke.”*

While only 7% of the respondents selected respiratory problems as one of the top three most impactful symptoms, those who had experienced it stressed how grave a complication it can be, sharing frightening stories of their constant vigilance to keep their child from choking to death. It may also be worth noting that although only one out of five individuals with CDD are male, three of those who described as having *“respiratory airway disease”* were young boys.

*“Currently, our biggest struggle is his respiratory health,”* said one of the panelists, mother to a 3-year-old son. *“We’ve taken two ambulance rides to the hospital for acute respiratory distress. His weak cough and his improper swallow contribute to his respiratory issues as he isn’t able to successfully clear secretions from his airway. He desaturates daily and needs to be connected to oxygen for varying lengths of time. [He] sometimes vomits when he seizes—from that first cough that indicates he’s about to vomit, I really only have seconds to get to him to try and prevent him from aspirating.”*

Some of the adolescent girls with CDD have had similar experiences. *“Recently, she’s been having problems clearing her secretions, particularly in the back of her throat. During a recent coughing incident, she choked on her own phlegm and it blocked her airway. She could not maintain her oxygen level, and this resulted in an ER trip which later turned into an admission when she was not able to breathe room air,”* the mother of a 10-year old girl said during her panel testimony.

While choking and blocked airway passages could quickly prove fatal, another respiratory danger comes from inhaling food or drinks, leading to aspiration pneumonia, which can also be life-threatening.

*“This year we noticed that the little cough was growing into little coughing fits, and they were getting worse. A swallow study revealed that she was aspirating liquids when she drank, her worsening aspiration meant even water was becoming a danger, not to mention solid food, so she had a G-tube surgically installed this summer,”* said the father of the 17-year-old girl during his testimony.

Similarly, the mother who worried about her son’s vomiting, added that *“when we combine something like having to deal with aspiration and the potential for any of these bacterial consequences to end up in his lungs, the vomiting, again, really makes for a very stressful family situation.”*

## J. Sleep problems

*“Fatigue and circadian rhythm dysfunction leaves him unable to stay engaged with activities that would help strengthen and maintain his skills and abilities. He loses stamina... and often gets sick with respiratory or GI illness. With dual sensory impairment, it is difficult for [him] to get on a schedule with his wake and sleep times. This is a known symptom of CDKL5 and tends to get worse with age and leads to children being awake for days on end.”*

While only selected by 6% of the respondents as being among the top three most burdensome symptoms, the *“all night sleep parties”* were also much discussed during the meeting.

*“She sleeps when she feels like it, and she's up when she feels like it. Sometimes she'll sleep through the day, but we've had times when she didn't sleep through the night, then she didn't sleep the next day, then she maybe slept half of the night the next night, and she was again awake. Whether she recognizes it, or we recognize it in her behavior, I know that it's affecting her biologically,”* one panelist said about her 17-month old daughter, during the facilitated discussion.

*“For [my daughter], it almost seems like it doesn't even bother her. Sometimes it's like she's the Energizer bunny and she's just going. Some nights, she's literally just awake and can't sleep. Some nights, she's screaming and crying, and cannot communicate what's wrong. So, you're trying to figure it out,”* said Utley, during the discussion session. But she added that there are dangers in trying to watch over a child when not getting enough sleep: *“If she is awake, I want someone paying attention.... I literally had done three days that I had had no more than five hours sleep. The next night, the first time ever, [my daughter's] 13, I slept through a major seizure, a big seizure. When I woke up, I saw the petechia all over her face, and I knew. I picked up my... camera that always is videoing. I went through [and] found it. It was a 10-minute seizure. That was the moment I said, ‘Okay, never again. If I've missed that much sleep, someone else is in charge for at least one night, so I can sleep.’”*

#### **K. Scoliosis (curvature of the spine)**

*“She is also showing signs of a curve in her spine, and I fear scoliosis may be in her future... [she] was recently diagnosed with pre-osteopenia.”*

Although only selected by one person as a top three most burdensome symptoms, at least one caregiver mentioned scoliosis in their child. *“She had a growth spurt, scoliosis [which lead to a] chronically dislocated left hip,”* said the mother of a 23-year old young woman. Others saw early signs (osteopenia) due to *“extreme hypotonia. My daughter's core is like a wet noodle,”* said one of the panelists.

However, others cited concerns about weakened bones that may precede later fractures and spinal issues. *“Decreased bone strength has been a persistent issue for her since she had a hip surgery,”* said one of the panelists, while another said that her 4-year old son *“was recently diagnosed with brittle bones due to his CDKL5 low tone and treatment side effects. His bones are like straws, hollow inside. We aren't able to access treatments yet as we need him to break a bone first for insurance approval.”*

## Impact on activities of daily life that the child cannot do or do as fully due to CDD

In the session's final multiple-choice polling question, participants were asked to choose the three specific activities of daily life most important to the caregiver or to their child that their child is not able to do or do as fully due to CDD. There were 48 respondents, and 144 responses to this question. Participants then expanded upon the polling results in the group discussion.

### A. Verbal communication (using words and sentences)

*"At one time, [she] had a vocabulary of about ten or so words, some of them made up, like, 'Psssh,' which means bus, the sound the air brakes makes. Her favorite word was 'mom.' Unfortunately, whether it's the effect of the anti-epilepsy meds on her brain, or the effect of the seizures themselves, she's lost the ability to speak almost entirely. One of the words she held onto the longest was 'beburber,' which the parent of any toddler will tell you means a McDonald's cheeseburger. She would shout out 'beburber' and squeal with delight when the car turned into the drive-through. She was looking forward to that cheeseburger, of course, but I think she was also excited because she felt like this was one area of her life that she could control."*

The most common selection of the polling question, chosen by 60% of the respondents, was the limited or inability to use words and sentences to communicate. In the above quote, the emphasis was on speech that was lost; several other parents noted that their children could not yet speak.

*"We'd like to be able to communicate and express to him what's going on around him, and we'd like to hear what he would like to do. He can't tell us, 'I don't like the sand. I don't like the way that feels,' or, 'That water doesn't feel good to me. That's too hot,'" said one mother.*

*"Our children are incredible human beings and that gets overlooked. We have our children who are looked upon as objects and problems to solve when really they're human beings and lovely souls and beautiful people and they're trapped from a communication point of view," said another mother.*

### B. Independence for most activities of daily living

*"He is 100% dependent on others to keep him alive."*

Almost 46% of respondents indicated that independence for most of the activities of daily living as one of the top three limitations that had a profound effect on their child—and on their own lives as well:

*"She needs to be fed, bathed, and dressed by a parent or nurse. She is not toilet trained. She needs to be carried to and from her bed or bath which is backbreaking work after doing it for ten years," said one mother.*

Such utter dependence on others has long-term implications for the family:

*"All of us not only deal with the fear of losing our child, we have another fear that I think is almost greater. And that is the fear of our children outliving us," said Utley in her opening statement.*

It may, in fact, become a burden that will be passed on to other family members.

*"I could list 100 effects CDKL5 has had on our family, but I'll close with this one," said the father who spoke on the first panel. "Recently, [my wife] and I were talking to our oldest daughter, about providing guardianship for [our daughter with CDD] once we're gone. She said, 'Don't worry, I've already decided that when I get married, I'm a package deal, even if that means I don't get married. [My sister] stays with me.' A young woman in the prime of her life giving up everything to care for her sister. That's the best and the worst of CDKL5, all in one."*

#### **C. Non-verbal communication (e.g., using gestures and facial expressions to communicate with others)**

*"Not only would I like to know what [she] likes to do, but also what's bothering her. Many, many times when she's crying, I end up asking a list of questions. "Does your head hurt? Does your tummy hurt? Are you hungry? Are you sad? What's going on?" Sometimes she will stop crying when I reach some option, and I'd like to believe there's a connection, and that when I reached the right answer, she stops. But I don't know if she understands. I don't know if she makes that connection. I would love to know, for her to point to her tummy, or to smile if I got it right, or to show me that she's connected."*

Close to 40% of respondents selected non-verbal communication as among the top three CDD-related limitations—suggesting their children are unable or have a severely limited ability to even use gestures or facial expressions to communicate.

*"[He] does not have a communication system, no way to have expressive or receptive communication. His cortical vision and hearing impairments are greatly impacted by CDKL5, and the dysfunction of his neurological system. He's not able to understand, or we're not able to communicate with him what's happening to his body, or what he would like, what activity, what he would like to stop, what he would like to continue," one of the panelists said. "That is very difficult for our family, and all of his caregivers and providers in school, and at medical daycare. It's very limited to crying, and of course it's hard to always know what that means."*

As fellow panelist said, there is no other solution but to guess:

*"My daughter is unable to communicate with me. I must guess if her crying stems from pain, hunger, or discomfort. It's an indescribably sickening feeling that I'm not able to ease my child's pain, or it's delayed because she can't tell me exactly where she's hurting or how it happened. There is no greater feeling of helplessness when a parent cannot help their child."*

#### **D. Using their hands to manipulate objects**

*"She used to be able to hold her sippy cup and use a straw. She was working, even though she has pretty significant cortical visual impairment, she was able to hold a spoon, use a brightly colored spoon, bring it to her mouth. She lost all of that during that period of intense seizure activity for almost a year. We're just starting to get her to think about holding onto a spoon."*

Use of their hands to manipulate objects was selected by over a third (35%) of the respondents as one of the top three most important activities of daily living that their child could not do or do as fully. As

mentioned by several caregivers, their children could not grasp objects or to use choice switches on communication tools.

## E. Social interaction and participation

*“When she was younger, it was a lot easier to get her out into the community. She was smaller. She was quieter. Society just isn’t real accepting of our children. That’s an additional burden that is very hard for us to talk about, or that probably gets overlooked in the conversation.”*

A little over a quarter (27%) of the polling participants prioritized social interaction and participation as one of the top three activities limited by CDD—due to challenges related to communication, mobility and/or behavior.

One caregiver on the second panel, whose daughter loves to go to a nearby Mexican restaurant, described how behavior challenges had resulted in fewer social outings as she grew older. *“Probably two times, I have overheard people complaining to management about [her] being loud. I do know that people aren’t always as accepting of some of the teeth grinding... There’s many different behaviors that can be very distracting, especially in public. It’s hard to deal with. It’s a very big chunk of what keeps some of us at home, especially as our kids age.”*

As one mother mentioned, one of the most difficult things for her child was *“seeing other children playing, and not being able to interact with them.”* Highlighting how important such interaction could be, another caregiver stated that *“peer and sibling interaction is probably one of my daughter’s biggest motivators. She is most likely to take advantage of the things that she’s learned in physical therapy (PT), occupational therapy (OT), speech therapy, vision therapy when she is interacting with her sisters, with our neighbors. She just comes alive, and it’s just so important for them to have peer and sibling interaction.”*

Though one of the other options for this polling question, **‘attending school or having a job (depending on their age),’** was only selected by a couple of respondents, the social engagement seemed to be the most valued aspect of the activity.

*“[She] is 23 years old, but the one thing that she loved to do was attend school. I think one of the saddest moments was to see her graduate, mostly because I knew that we were going to be her life. She no longer had friends. No one that was similar to her,”* one mother said during the discussion.

The father of the 17-year-old had a similar observation: *“She loved her special needs class at the junior high school. Then, when it was time for her to move up to high school, we went to a meeting where her new special needs teacher explained how the program was focused on things like life skills, learning Washington State history, etc. There was no program in that district for children of more limited skills. My wife left the meeting in tears. We sold our house and moved to a better school district for [her].”*

Changing school districts is not an option for those out of school, so the family of the 23-year old young woman has tried to find other channels for social interaction: *“We have one nurse who will take her to Walmart or someplace, and so she does get to have some socialization,”* her mother said. However, she added that CDD still limits on these activities: *“What happens when she has gone to the bathroom in her diaper? When you have a little one, it’s not too hard to change them in the bathroom, but when you*

*have someone who's 23 years old, 80 pounds? Even though she's not a big girl, where do you change her pants? Those are some of the most difficult things for us right now."*

#### **F. Feeding oneself**

*"We were starting to work on self-feeding [but she lost all of that]. Has no interest whatsoever in using a straw again or holding onto the sippy cup. Everything has to be given with fluids. She's gained some back, but what took about four weeks of intense seizures to lose has taken us close to eight years to regain, even close to it."*

A quarter of the polling participants ranked self-feeding as being one of the top three most important activities of daily living CDD kept their child from doing fully.

#### **G. Walking**

*"Another way CDKL5 impacts [her] is by limiting her mobility. [She] was lucky to be one of the CDKL5 kids who could walk. And she loved it. One of her favorite activities was to go to the mall and walk or even run down the aisles. It was a challenge for us just to keep up with her. Sadly, in recent years, she's become more and more unsure in her steps. Walking is very limited. She falls frequently. Running is nothing more than a memory."*

A quarter of the polling participants also highlighted walking as a one of the top three activities limited by CDD. Only a few referred to their child being able to walk at all—only one who said their child had once been able to do it well.

#### **H. Sitting unaided**

*"Our daughter is 23 years old. She does not bear weight. She does not sit up alone."*

A similar proportion of the respondents (21%) selected sitting unaided as one of the top three activities their child could not do as fully due to CDD. One of the panelists from the first session described having to prop her son up to sit, a skill which he then lost. A panelist from the second session described how her 13-year old daughter now finds it difficult to sit comfortably due to use of a device that immobilizes her knees to prevent her weakened bones from fracturing during seizures.

#### **I. Have regular sleep patterns**

*"When she was little, she used to go through phases where she wouldn't sleep for days, or it seemed like days on end. Then things really, really improved. But just lately, probably in the last six months, she can go for at least four nights a week where she's having an all-night party. Sleep is a little bit more impacted as she's moved into puberty."*

Having a regular sleep pattern was selected by 15% as one top three activities limited by CDD. Some attributed this to disturbances in circadian rhythms, others to hyperactivity.

## J. Other issues mentioned related to the burden of CDD

*“I also feel stressed, stressed because the majority of his caretaking is done by me, stressed that we need to find private nurses to babysit because grandparents can’t do it anymore and our private insurance doesn’t cover any nursing.”*

Although not listed as a question on its own, many of the participants discussed the burden of caregiving on the parents and family— and the toll on their psychosocial, emotional and physical health. Several caregivers said they were traumatized by the diagnostic journey—others by the trauma dealing with their child’s life-threatening emergencies—and this was not limited to the parents.

*“I get anxious that he could have a very big seizure, and he could end up in the hospital for a very long time. I’m anxious and I’m curious about when my brother goes to a hospital with my mom because I don’t know what’s going to happen,”* said the young brother of one boy with CDD.

One of the panelists described how being *“subjected to unimaginable mental and physical stress”* had made her physically ill: *“As caregivers, we want the best for our children and spend every minute trying to figure out how to make it better. The mental fatigue, combined with the physical stress of caring for an immobile child and the many sleepless nights, definitely takes a toll on the body. Earlier this year, I was diagnosed with a cardiac issue known as PVCs (premature ventricular contractions), which are increased irregular heartbeats. I was told this condition was the direct result of stress and lack of sleep. Fortunately, I was able to have a surgery which involved cauterizing several areas of my heart.”*

Another young mother spoke about how, after a few nights of interrupted sleep, she begins to neglect her own needs: *“I also don’t want to get out of bed, but I have to. I don’t do anything that doesn’t have to do with her. I change her. I feed her. She’s absolutely taken care of, but I forget things sometimes. Even things that have to do with her, I do last minute. That’s not my style. I haven’t missed a therapy appointment for her yet, but I’ve missed other things for myself. The house hasn’t been cleaned maybe timely, or we have to order in, because I don’t have time or energy to cook, or things like that. I don’t feel like doing anything that doesn’t have to do with her. That’s very distracting. That’s very disappointing. That doesn’t make me feel great. I feel like I spend days in a haze, where all I do is just watch her.”*



## Topic 2: Caregiver perspectives on treatment/management of the condition

The second topic focused on experiences, positive or negative, with current treatments, supportive care and medical devices used to help manage CDD as well as hopes for future approaches to treatment.

### Panel testimony

A panel of five caregivers led off the session (short descriptions of the panelists' testimonies are provided to give a sense of their child's care and their goals for treatment—many of their comments are integrated elsewhere in the report by topic):

- The first caregiver, the mother of a 5-year-old girl, diagnosed at the age of 4 months described the enormous burden of care for her child: the AEDs she has tried, her ketogenic diet and a long list of supplements, her surgery to place a G-tube *"after losing her safe swallow"* and the variety of other medications to manage GI-problems. *"Each of these drugs have their own dosing guidelines. Some need to be taken before food. Some need to be taken with a meal. Some are taken three times a day while others are taken twice a day. All in all, we give [her] a dose of medication at six different times throughout the day, which interrupts her normal learning and play. Additionally, each of her meals is considered a dose of medication."* The benefits of all these treatments seem limited: *"[She] still has four to six big seizures a day. She still suffers with GI issues. We still find ourselves cleaning up vomit and having to give her suppositories to induce a bowel movement."* But with all these efforts to manage seizures and GI issues, she said what she would most want from a treatment would be to better communicate with her daughter.
- The next panelist described her *"almost 14-year-old daughter"* as being *"on the more moderate to severe side of the CDD spectrum in some respects but... blessedly... spared other challenges of the disorder."* Nevertheless, her daughter has cycles of seizures linked in some way, possibly even triggered by, episodes of *"constipation and severe abdominal cramping,"* and although once able to stand *"well with very minimal assistance at the hip for 30 plus minutes"* this is now compromised by *"decreased bone strength."* The caregiver said her daughter's diet and supplements reduce not only her gastrointestinal problems but also her seizure frequency—and believes therapies that could provide even modest improvement function could yield significantly improve her quality of life. For instance, treatments that increase bone strength could help her daughter stand longer and perhaps walk with assistance. She also described how access to an adaptive communication device to her vision therapy helped her daughter indicate preferences and helped her share her favorite color: Purple—revealing part of her personality. *"[Making] inroads into addressing gastrointestinal motility and cortical visual impairment would benefit her the most on a daily basis,"* the caregiver concluded.
- Panelist 3 was the mother of 4-year-old boy with *"dual impairments [sight and hearing], physical delays, and intractable epilepsy."* He *"has tried six different combinations of AEDs,"* [at the time of the meeting, he was taking two] *"with the ketogenic diet and additional multiple medications (to counteract the effects of his diet and the AED by keeping his organs and body functioning). Additionally, he has multidisciplinary therapy sessions; physical, occupational, speech therapy, and reflex integration. He sees 17 specialists at two children's hospitals in two different states."* Despite all this, seizure duration, intensity and frequency have only decreased somewhat: *"Our son's*



*cognitive impairment, vision and hearing impairment, feeding delays, GI, nonverbal status, and physical impairments have remained severely delayed with very little development or progress.”* She wants her son’s symptoms to be managed *“to a level that allows [him] to progress in a way that is meaningful to him.”* In addition to better seizure control and neurological development, her other goals for his treatment were *“improvements in hypotonia, physical skill development, improved language acquisition, sleep patterns, and organ body function.”*

- By the time the next panelist’s daughter was diagnosed at age of 6 and a half years, *“she had endured thousands of seizures and failed most available AEDs.”* At the meeting, her mother said she was *“14 years old and attend[ing] a public education school with a focus on augmentative and alternative communication or AAC. Currently, [her] maintenance AEDs include divalproex sodium, clobazam, diazepam and an investigational drug.”* Although some of her treatments worked for a short while, their benefit waned. Furthermore, she said her daughter *“experienced serious and life-threatening side effects from drugs used to treat epilepsy,”* recounting some harrowing episodes including status *epilepticus, a severe hypersensitivity reaction and other sequelae (see thematic review)*. Eventually her condition stabilized but *“as [she] neared the onset of puberty, we again lost functional seizure control. We prioritized her abrupt need for a spinal fusion over a vagus nerve stimulator placement, leaving us with few opportunities to address this decrease in her quality of life.”* However, she had an opportunity to enter a clinical trial, and the new treatment eventually led to a marked decrease in seizure count, and *“to our surprise and delight”* improvements in several other functional domains (behavior, motor function, eye control and communication).
- The final caregiver on the panel provided testimony using first-person narration from the perspective of his 12-year-old granddaughter, who is *“constantly impeded by... disabilities, not the least of which is... intractable epilepsy, motor impairments and... a cumbersome eye gaze talker.”* At the time of the meeting, her treatments included two AEDs, PT, OT, speech, and music therapy. *“We have tried approximately 16 antiepileptic drugs. Think about that. 12 years, 16 meds... It has been a lifetime of titration and side effects.”* Some of this was due to *“well-intentioned MDs possessed with solving each and every seizure problem, as if that was my only problem.”* She has other unmet needs. Her caregivers and therapists see that she is *“capable of clear, deliberate, intuitive thinking, and occasionally biting humor. It is my transmission that is broken.”* As a goal for future treatment, rather than symptom control, the focus should be on the root cause of CDKL5 deficiency. *“I want you to know that we are trapped... My neuronal system needs to be rescued and restored, and I will do the rest. I want to walk and talk without the fog of drugs. With greater strength in my vocal cords and limbs, I may learn to talk and walk and grow just like any other child does.”*

The panel painted a bleak picture of current treatment options for children and young people with CDD who even before diagnosis start being cycled through AEDs, sometimes combined with diets (ketogenic or Atkins) which at best work only for a short time and yield only partial benefits, often at a cost of making some of the child’s other symptoms worse and decreasing engagement and skill acquisition. At times, AEDs have caused life-threatening reactions and dramatically increased seizures. And yet, families have little option but to try to them, in order to find a treatment that manages their child’s seizures as well as possible for as long as possible—at least partly because the seizures increase other CDD symptoms such as hypotonia, motor functions, eye control, GI issues, swallow function and cough.

Management of these health conditions are also symptomatic, with medications (for GI issues), enteral feeding (including G-tubes), medical equipment and aids (cough assist, suction, eye gaze communication devices), mobility equipment and home adaptations and accommodations that help children move (or

be moved) from place to place. Panelists have used PT/OT to improve motor and physical function and other guided and complimentary therapies that attempt to reach and engage their children.

But while everyone wants better treatments for CDD symptoms and effective seizure control without debilitating side effects, many emphasized that neurological and developmental delay underlying CDD remains completely unaddressed. Ultimately, future interventions that address the CDKL5 deficiency may offer most hope for treating the broad but interconnected spectrum of symptoms seen in CDD.

After the panel, the experience of caregivers and their children with the pharmacological and multidisciplinary care and therapies for CDD— as well as what they want from future treatments—were explored in a more systematic way by the polling questions and the facilitated group discussion.

### The effectiveness of treatment and care of existing therapy for CDD

Note: Some liberty has been taken with the order of these questions, to best reflect what caregivers had to say about how CDD is currently managed. To highlight the unmet needs that clinical development programs must address, polling participants were asked—through a modified Caregiver Global Impression of Change (CaGI) scale—how much any of the medications or therapy helped improve their child’s quality of life. There were 43 respondents and 43 responses to this question.

Only 16% of the respondents indicated that available treatments had substantially and 9% moderately, improved their child’s symptoms; 5% reported not being sure if there had been improvement and another 5% responded that there had been no change. Strikingly, 65% reported only slight improvement—which suggests that most families are finding little relief from this profoundly devastating disorder.

The inadequacy of CDD treatment benefits must also be placed in the context of the downsides of treatment, which, as some of the panelists in both sessions stressed, could be life-threatening at times.

As one mother had already discovered: *“Every treatment decision that we make seems to have detrimental effects in other areas,”* when her child suddenly stopped eating: *“We realized later it was surprisingly related to her treatment management. We chased seizure freedom by meddling with her medication and medical diet, and we obtained it temporarily, at the price of refusal to eat or drink.”*

The following two polling questions addressed how widely treatments and therapies are used—and this report uses the order of their responses to present what meeting participants had to say about the benefits and shortcomings of each intervention. The final question addressed the unmet needs caregivers most want clinical development programs to address.

### Experiences with prescription treatments and supplements

The session’s first polling question asked participants to indicate all the medical interventions that their child was currently using. There were 46 respondents and 165 responses to the following options.

## A. Anti-epilepsy drugs [AEDs]

*“[She] was diagnosed just before her fourth birthday, and at that point, she had been on 21 therapies for seizures...”*

By far, the most commonly used medications were AEDs (including Epidiolex). This option was selected by almost every respondent (98%).

Many individuals with CDD had cycled through several, and some more than a dozen AEDs: *“She was on maybe 12 or 14 different drugs over her lifetime,”* said the mother of the 23-year-old woman with CDD; *“16 different meds,”* said the mother of the 12-year-old whose grandfather represented her on the panel, versus 21 used before the age of 4 years in one girl. Some may have had epilepsy more refractory to treatment than others, but even were that not the case, one could quickly work through most if not all the available options if an AED was only used a year or two before switching treatment.

*“AEDs have provided [her] relief for only short periods if they work at all,”* said the panelist whose daughter had failed most of the available options before her diagnosis at the age of 6 and a half years.

As another panelist, whose daughter had *“tried and failed four different antiepileptic drugs”* explained, *“some of the [AEDs] we have tried have worked for a while, and then their efficacy has dwindled slowly. She was on Topamax for years. We saw a stunning improvement in seizure control when she first started the drug as an infant, so we put up with the major side effects of appetite suppression, heat intolerance, and acidosis. But slowly over the course of two years, the seizures crept back in, getting longer and more intense until she ended up hospitalized.”*

Treatments do provide partial benefit—reducing the severity or frequency of seizures. The girl who failed 21 therapies in early childhood, now an adolescent, found some benefit *“when she was four, on vigabatrin. She went on a dose of 1500 milligrams a day. She's only recently gone up to 2000 milligrams a day. For her, that was her miracle,”* said her mother, though she added that her daughter is now on a combination of treatments including VGN, a low dose of Keppra and the experimental drug ataluren.

There was positive feedback on some of the more experimental treatments—as well as Epidiolex (FDA-approved for other refractory epilepsy).

The mother of the 23-year old girl who said that since starting on the highly purified cannabidiol extract: *“We have since taken her off the other seizure drug. She is only on Epidiolex. It has cut her seizures over 60% and continues to do so. It gives her days; she sometimes has a week without a seizure. She smiles. She is clearly happier. Even though she can't speak to me, she is clearly happier.”*

*“We too were able to come off the other drugs,”* said one of the panelists during the discussion, while the mother of the 8-year-old boy said: *“We started about four months ago. It's reduced GI issues and when I come by [him] now, he actually reaches out for me and puts his arm towards me, which is an enormous obviously improvement for him from a cognitive perspective. He knows that I'm there.”*

Indeed, reducing epilepsy severity might improve other symptoms. However, it has yet to be seen if these benefits will be seen more widely in the community or whether they will also diminish with time.

Sometime AEDs make the seizures dramatically worse:

*“Some of the drugs we've tried made it clear very quickly that they were not the drug for [her]. In the case of Keppra, the medication made her seizures skyrocket to over 100 a day,”* said one of the panelists.

*“When vigabatrin was weaned and Vimpat added as her main medication [it] led to uncontrolled daily seizure activity and an almost complete loss of her ability to swallow,”* said the mother of a 14-year old.

*“Before her CDD diagnosis around age four, she acquired electrical status epilepticus during sleep caused by oxcarbazepine. It led to the addition of high dose diazepam at night that continues today,”* said the panelist whose daughter was diagnosed at age 6 and a half years. But this was not her only life-threatening adverse event. *“At age 10, she narrowly escaped liver failure from a severe drug hypersensitivity reaction known as drug rash with eosinophilia and systemic symptoms—or DRESS syndrome—shortly after we introduced a second-generation AED adjunct therapy of rufinamide. DRESS syndrome is rare and not well understood. There are no treatment options other than withdrawal of suspect drug and high dose steroids. It took a four-month treatment course of prednisone to bring her liver back to baseline from near failure.”*

Management of this event had another potentially fatal clinical consequence: *“A few months later, she contracted mycoplasma pneumonia that triggered a 20-day hospital stay including 14 days in the PQ. Ten of those days were spent intubated,”* the caregiver said.

Even when the AEDs offer some relief from the severity of the child's epilepsy, their side effects may make other CDD symptoms worse.

For instance, vigabatrin (Sabril), the drug that worked so well for one girl caused problems for the baby with CDD represented by topic 1's first panelist: *“She stopped seizing on Sabril. Four days later, she was still refusing water, any liquids, any food. We took her off, [and] the next day she started eating.”*

*“One of the medications we failed on was valproic acid. It actually did reduce her seizures a little,”* said Utley, mother to a 13-year old girl. *“The teacher and the therapist were saying, ‘Her eye contact is amazing... her attention span is better.’ And that was great, but she had a very strange and evidently rare vestibular reaction—she stopped walking. Which would you rather: walking or attention span? That was a drug we weaned.”*

Another mother of an adolescent girl stressed that they preferred to use *“low dose drugs, not drugging her up to the point where she can't learn, and she's sleeping all the time.”*

This AED effect on cognition and alertness was mentioned by others as well.

*“The side effects of the meds have more effect on her than the actual antiepileptic effect. What I mean by that is the drowsiness,”* said the mother of the older adolescent girl whose grandfather spoke for her on the panel. *“You lose that clarity with the medications. Even if you gain seizure control for a week or two weeks or, if you're really lucky, a whole month, you lose that clarity and the interaction with the kids. That's actually the hardest part... You have to weigh: do you want your child to have quality of life and to be interacting and eating and functioning with you or do you want them to not be seizing?”*

These testimonies show the effectiveness of AEDs is limited or of short duration and often outweighed by the risks of treatment. There is no standard of care therapy, and different AEDs can have markedly

different effects in different children. Treatment is individualized, or, put another way, trial and error. As the grandfather caregiver said: *“Each [new AED] requires a titration period, all with varying side effects. Some side effects require the meds be stopped. Others require an adjustment period to get through transitory side effects or, in the alternate, a weaning off period and subsequent search for a new drug to begin the cycle again.”*

## B. Supplements

*“[She] takes five supplements: a multivitamin, calcium, vitamin D, magnesium, and selenium as well as a daily probiotic to compensate for the vitamins and minerals missing in her diet.”*

Supplements were the next most common medical interventions, used by 72% of individuals represented in the poll to correct nutrient deficiencies due to their diet and medical treatments. There was no discussion about whether dietary supplementation improved clinical outcomes.

## C. Sleep medication

*“We’ve tried different things to help her sleep. Melatonin. I know the other parents have tried even harder medications, and they don’t seem to always have an effect.”*

Nearly half (46%) of the individuals represented in the poll use some form of sleeping medications to help manage the sleep disturbances associated with CDD.

*“I couldn’t deal with the night parties. I need my sleep,”* said one of the panelists, mother to an 11-year old, who achieved relief using clorazepate. *“She sleeps beautifully about eleven, twelve hours a night, and I get sleep every night as a result of it. Obviously, the dose has gone up over the years. She goes to school every day, gets up and functions. We tried a series of other drugs, and nothing worked. Melatonin didn’t work. Ativan didn’t work.”*

## D. Ketogenic diet

*“The ketogenic diet is a particularly difficult treatment to evaluate efficacy because it can take a very long time to work. When we first started it, we noticed some seizure reduction, but the real reason we are still on it is that we immediately noticed some increased cognitive ability. She made better eye contact and was able to focus on tasks for longer. We are still on the diet because, frankly, we are afraid to remove it and risk losing this effect.”*

The ketogenic diet, which has been demonstrated to offer benefits to some individuals with refractory epilepsy, has been tried or is being used by about 37 % of the individuals represented by polling respondents. Others may be put off by the demands of the diet.

*“She’s on the very strict ketogenic diet. Her diet is 90% fat, 7% protein, and only 3% carbohydrates, so no Halloween candy this weekend for our little girl,”* said the mother of one 5-year old girl. *“Each of her meals is considered a dose of medication. For the ketogenic diet, we need to weigh everything to the tenth of a gram and ensure that she eats it in its entirety within 30 minutes.”*

One risk is that getting the proportions of the diet slightly wrong could lead to adverse events.

*“When we increased the ratio, she stopped seizing completely,”* said the mother of the 17-month-old girl on the first panel. *“We thought [the diet] was our miracle until she stopped eating, and she became over-ketotic, acidotic, hypoglycemic. We ended up in the hospital, had to take her off of that ratio down to the older ratio. She started seizing immediately, but she went back to eating.”*

And yet, others keep their child on the diet despite its perceived downsides: *“His diet impacts his ability to gain weight and grow at a typical pace and impacts his kidney, liver and GI function. Both [diet and AEDs] result in him needing to take additional medications,”* said the caregiver of the 4-year-old boy.

As a few caregivers indicated, they are afraid to go off the diet and losing its perceived benefits. This included the mother of the 17-month-old girl: *“We started it at six weeks. We were required to stop breastfeeding, which was absolutely heartbreaking for us. At the time, we were in the hospital and we did notice an improvement in her cognitive abilities, attention, and awareness. The seizures were never completely gone for long periods of time. The longest was 12 days that we had seizure freedom, but we are not taking her off because we don't want to lose the potential cognitive benefits.”*

One panelist reported benefits from similar diet, the modified Atkins diet, that is less restrictive, but still with a high fat content: *“One of the main interventions that has improved her seizure control the most has been the modified Atkins diet [which] has improved her seizures by 60 to 70%, although it took close to a year to see the full benefit.”* The only time that her daughter was not on the diet was when they switched her AED which immediately aggravated her seizures. Although they quickly switched her AED, *“she only regained good seizure control, one seizure every four to five days, once she was fully back on the modified Atkins diet.”*

## E. Others

*“To combat excessive reflux and vomiting, she takes ranitidine and omeprazole. She also takes a low dose of erythromycin to help her with gastric motility... We [have] to give her suppositories to induce a bowel movement.”*

Approximately 33% of the polling respondents selected ‘others,’ reflecting the complexity of managing the many complications over the course of a lifetime with CDD.

Many mentioned GI medications, *“numerous stool softeners, laxatives, and enemas.”* Similarly, another caregiver said that her son *“takes four different medications, Carafate, Nexium, Pulmicort ingested.”*

As with the other medical interventions mentioned, treatment is individualized with experimentation and dose adjustment to get the balance right: *“Every day we... walk the fine line and second-guess ourselves about the quantity of MiraLAX to administer,”* said the father whose daughter has constipation alternating with diarrhea. Similarly, the caregiver of the ‘almost 14-year-old girl’ said, *“Over the years, to help with the constipation, we've had to continually adjust the approach. High fiber foods, adding fiber supplements, probiotics, magnesium citrate... Her body seemed to acclimate to each change, and she required more to maintain some degree of regularity. It was not until she was prescribed Senna at the age of seven that we saw a more consistent resolution to her constipation.”*



## F. Formulations of medical cannabis including CBD

Almost 26% of respondents indicated that their loved one was using a formulation of medical cannabis, but aside from, the pharmaceutical Epidiolex, none commented on this during the discussion (there was some feedback on them during the post-meeting survey however).

## G. Vagus nerve stimulator (VNS)

*"[After improvement with an AED], she had the vagus nerve stimulator (VNS) placed. She's now on her third. Within two years of the VNS being placed, she no longer had tonic spasms. Her seizure type is non-motor, so nine years, she's been tonic-free. [Though] we know that when the battery starts running out on her VNS, she starts to have stiffening creeping back."*

A little over a quarter (24%) of the respondents indicated that they had an VNS implanted in their child to reduce the most severe seizures.

## H. Experimental medications as part of a clinical trial/expanded access

*"She started a single use compassionate trial of ataluren earlier this year... and the morning seizures she used to have on wakening, which would be quite long absences, up to 20 minutes long, she no longer has them. She might have the odd [one] but certainly significantly improved on this nonsense mutation drug."*

About one of five (20%) of the population in the poll have had access to experimental medications as part of a clinical trial or expanded access program—a surprisingly high proportion given the small number of trials in patients with CDD. Ataluren and ganaxolone were two mentioned by name.

Feedback largely seemed positive, though it is not yet possible to assess duration of benefit or risk of long-term side effects, particularly in the context of polypharmacy in a child who is maturing physically.

*"We're into about four or five months of starting that drug [ataluren]... I think since it kind of coincided with that, so I'm not sure if it's an effect of the drug that actually her overall mood has improved—but because her overall mood has improved, she's just wired quite a lot of the time—or whether it is because she's just about to enter those womanhood years,"* said the caregiver of one adolescent girl.

## I. Steroid treatment

Two polling respondents indicated their child had had steroid treatment, which is often used for the management of infantile spasms.

## J. Neurosurgery

None of the caregivers in the poll had to resort to neurosurgery for their child.

## Experiences with multidisciplinary care to treat the symptoms

The next polling question asked about all the other types of multidisciplinary interventions and therapies used to help manage the symptoms of CDD. There were 49 respondents, and 365 responses to this multiple-choice question, representing a substantial investment in time and effort to obtain often small changes in their children's health and quality of life. The order of the polling responses has been rearranged slightly based on related or interconnected modalities.

### A. Approved pharmacological therapies (e.g. approved antiepileptic drugs)

Largely covered in the preceding thematic analysis, approved pharmacologic drugs, such as AEDs, were the most commonly selected option (chosen by 94% of the respondents), while other options reflected the wide range of multidisciplinary therapies and equipment used to support those with CDD.

### B. Physical and occupational therapy

*"You get all these therapies, and you feel like your child is getting ready for the Olympics or something, but actually, it's what we need to do until we have some kind of treatment or hopefully, one day, a cure, to just give them better quality of life."*

PT and OT are used by approximately 90% and 84%, respectively, of the individuals with CDD represented in the poll. Along with the standard therapies to increase a child's strength, control and range of motion (and vision), a few novel modalities were mentioned by panelists and during the discussion, including *"TheraSuit therapy"* and electrical stimulation therapy (stim therapy).

Caregivers described how these therapies offer incremental but nonetheless meaningful benefits.

*"With PT, when given proper trunk support, he was able to keep his head up in midline for a few minutes, on a good day. And around age two, if you set him up just right, he was able to prop sit for a few seconds on his own,"* said the mother of one 3-year-old boy.

*"It's really helped him to increase his head control, and with increased head control comes increased respiratory secretion management, upper GI, lower GI motility improvements, so it's something that we've really enjoyed,"* said another mother, caregiver to a son who has been using stim therapy.

The primary downside appears to be the time devoted to treatment, *"the lack of flexibility in his schedule due to his therapy, medication, and feeding,"* said the mother to a 4-year-old son.

*"[She] has therapies basically every day for a few hours, and I feel it's such a blessing that we're able to give her the therapies that she needs, but it takes a turn on her social life. She misses out on spending time with her siblings or going with us to places,"* said the mother of a 5-year-old girl. *"It's just a way of getting her to move. You can see the children enjoying being moved, whether they're taking steps or helping them sit up. It's a balance, but we keep going as long as she's enjoying it and shows progress."*



### C. Speech therapy and eye gaze speech production device

*“Communication is a fundamental human right, and the barriers of access to these systems are steep for intellectually disabled people. Identifying specialists with the skills to appropriately assess, fund and implement AAC systems is a tall order.”*

Four out of five respondents (80%) indicated some form of speech therapy was used by the individual with CDD that they represented. Given that speech and other forms of communication are severely limited for many with CDD, an array of speech therapy modalities are employed including AAC systems such as the eye gaze speech device, selected by 33% of participants during polling.

Caregivers were enthusiastic about what this therapy could potentially offer: communication beyond simple yes/no responses but acknowledged can using the devices effort, and children often grow tired.

*“Using your eyes to communicate takes an incredible amount of muscle control and motor sequence planning, as well as highly specialized speech and language therapists,”* said one of the panelists. While the caregiver who provided third-party narration for his grandchild stated, *“I think quite clearly and speak quite clearly with my eye gaze computer... but it is cumbersome and tiresome to use because of the calibration issues.”*

Calibration of the devices currently require conscious cooperation by the user.

### D. Mobility equipment (adaptive strollers, wheelchairs)

*“We will become well-versed in all types of durable medical equipment, including wheelchairs, standers”*

Some form of mobility device was used by approximately 73% of the individuals with CDD represented in the polling. While this equipment does help children and adults with CDD participate in activities with their families and engage more with society, caregivers also noted their limitations.

*“[Her] impaired mobility limits more than just trips to the mall. Her bulky stroller, really a type of wheelchair, makes it a challenge to take her into crowded spaces,”* said one caregiver whose daughter has recently begun to lose the ability to walk. *“It was a difficult and sad decision not to take her to our church's Halloween party this year [knowing] she'd be confined to her stroller, and the thought of pushing that through the crowd of young children is daunting.”*

### E. Modifications/accommodations at home

*“We're getting a handicapped accessibility for her room and bathroom to include a ceiling lift and a walk-in shower. An accessible wheelchair van will soon follow.”*

The next most common intervention to improve their child's quality of life, selected by 67% of the polling participants, were accommodations and modifications to the home.

*“Our home has become a live-in therapy and care facility. It's not a typical home because of [his] needs,”* said the mother of one 4-year-old boy, whose family has gone to great lengths to reach him. *“[He] has a soft play area where he's able to explore and interact with switch toys in the hopes that he will learn cause and effect. He has a hammock-style swing that hangs from a ceiling in our dining room. This helps*

*him receive his vestibular input that he needs often. He has a little room to help teach him spatial recognition and to help him understand that there's a world around him."*

Making these modifications take time, effort and comes at considerable expense. *"Putting a ramp on our house... took six months of planning and then another year and a half for it actually to get on the house,"* one caregiver said.

#### **F. Orthotics support (back brace, foot braces)**

*"She had a hip surgery in 2015 for a progressing subluxation of her right hip. Unfortunately, the stiffness of her bones and the stiffness of the plates were not good matches during the strong tonic muscular contractions at the start of her seizures. She has suffered four complete fractures of her right femur around the plates."*

Orthotic support and other orthopedic interventions are also commonly used, according to 65% of respondents. Several participants mentioned braces in passing, and, while not a device, other manual forms of support often are necessary, *"the nurse positions [her] several times a day to protect her spine and pelvis,"* said the mother of the 10-year-old girl on Panel 1. Finally, with increasing bone weakness and scoliosis, surgical interventions may even become necessary (one of the panelists stated that her teenaged daughter had *"an abrupt need for a spinal fusion."*)

As with other accommodations, expense and accessibility are downsides: *"The amount of time it takes to get equipment. We've learned to start a year ahead of the time when [she] needs a new chair or needs new orthotics because it takes that long for her to actually get the new product."*

#### **G. Recreational therapies, such as hydrotherapy (water therapy), hippotherapy and music therapy**

*"Every time she was in water therapy, even the one time she was extremely fussy, you could tell she really enjoys it. It usually helped calm her down, and she learned to do things in water that then she was able to transfer on land that we'd never seen her do before. For instance, moving. Learning that moving her body is an enjoyable experience. She was a lot more still before we took her to the pool, and then we noticed that she was starting to move in her playpen on land, move her limbs, maybe even try to roll or reach, which she started to do first in water."*

Two of the polling options were for recreational therapies that can serve as an adjunct to other forms of PT, though, based on the discussion, others are in use as well. About 43% of the respondents selected water therapy as one of the multidisciplinary therapies used for their loved ones, and one that was particularly enjoyable: *"He really enjoyed swimming."* Meanwhile, though less commonly selected, about 14% had some experience with hippotherapy.

One caregiver with a 23-year-old daughter unable to sit on her own, highly recommended it: *"When we put her on a horse, she would droop forward. As soon as it started to walk, she sat straight up. It was wonderful. We did this for several years,"* she said, though they discontinued the therapy once the young woman started having hip problems.

Although not listed as a polling option, during the discussion music therapy was mentioned: *"That is the one therapy that [my daughter] consistently meets her goals in. No matter even if she's had seizures,*

*when that music therapist comes in, she will participate. She will pay attention. She will love it,”* said one caregiver—and a number of other audience members at the meeting murmured in agreement.

#### H. Nutritional support (nasogastric tube, g-tube) and ‘others’

*“Not only does he have a G-tube placed...he has to have an annual upper GI and lower GI scope [and] when he does vomit or he has a wet burp, he will go into just really bad spasms in the airway. It scares him to death. He can’t breathe. He’s got mucus that backs up because of it. We have to get suctioning in place immediately”*

Roughly the same percentage of caregivers participating in the live-polling indicated that their child was using some form of nutritional support (nasogastric tube, g-tube) (39%) or other forms of multidisciplinary care (40%)—which based upon testimonies and discussion, often involved respiratory support, as well as other interventions.

Caregivers spoke about having to resort to placing G-tubes in their child after they lost the ability to swallow, *“She had surgery in 2018 to place a G-tube after losing her safe swallow during an episode of status epilepticus,”* said the caregiver of a 5-year-old girl. *“Right now, he is 100% fed via G-tube,”* said the mother of a 3-year-old boy who after infections and worsening seizures, *“wasn’t strong enough to eat by mouth.”*

As the father of an adolescent girl said, during the discussion, the decision to have a G-tube placed in your child can be a difficult one: *“The G-tube is the one that we probably fought the longest and in hindsight, I don’t know why, looking back, we waited so long. Her seizures come in cycles... and she has two, three, four, five days where she’s not eating; she’s not drinking; she’s just having clusters of seizures. The G-tube allowed us to get food and fluids and medicine in her when she’s having those bad periods. And that certainly has been probably the biggest improvement in our care-taking and in her life.”*

And yet the family’s initial reluctance was telling: *“it’s always hard to schedule a surgery, to put that on the calendar for your daughter,”* he said. G-tubes are invasive, and no parent wants to have to resort to the procedure to save their child’s life. But that is a decision many are forced to make with CDD.

It also may not stop there.

*“She had a G-tube surgically installed this summer,”* said the father of the teenaged girl with alternating constipation/diarrhea. *“When [she] was having her G-tube inserted, the doctor suggested also having an appendicostomy so we can administer enema fluid straight to the top of her colon. New procedure, same question: ‘How much do we give her tonight?’”*

Additionally, many children who have lost their swallow are at risk of choking, aspiration pneumonia and being unable to clear mucus or cough. They require respiratory support.

*“He desaturates daily and needs to be connected to oxygen for varying lengths of time,”* said the mother of a 4-year-old boy. *“He takes medications to manage his respiratory airway disease, and controlled home suction to keep his airway open,”* said the mother of a boy aged 4 years. Then, during the discussion, a 9-year old boy’s mother who said she often must rush to school to suction him added, *“from a nursing perspective, the nurse suctions him pretty much every hour.”*

This raises an aspect of the care burden not specifically covered by the live-polling questions: the amount of the professional care children routinely need to function and survive. As this and other comments suggested, many caregivers rely on nursing care—or would if they could. “[She] goes to school every day with a private duty nurse. In addition to monitoring her daily seizures. The nurse is our piece of mind while my husband and I are at work,” the mother of the 10-year old girl said.

“We are lucky enough to have nursing care for a few hours every day, except weekends,” said the mother of a 23-year old young woman.

However, such care is not always accessible. “Our private insurance doesn’t cover any nursing,” said the mother to a 3-year-old boy with a G-tube and respiratory issues. Whether this is a cost-effective stance for an insurance company to take is another matter—considering the possible alternatives: “We’ve taken two ambulance rides to the hospital for acute respiratory distress,” the caregiver said.

Many mentioned trips to the emergency room and hospitalization. Caregivers also referred to the variety of specialists that their child must see: “She now needs to be followed by pediatric physiatrists and endocrinologists for treatment. This would be in addition to being followed by her pediatrician, neurologist, gastroenterologist, orthopedist, and nutritionist,” the mother of the 10-year-old girl said.

All the ER, clinic visits and specialist care exact a toll on families. As the caregiver who takes her son to see 17 specialists in two states said: “The cost to our time, our car, our family are hard to put into words.” Another caregiver framed the burden of from the perspective of what it takes to travel: “We pack her pump, her formula, her scale, and her blender. We pack her medications, her syringes, her pulse ox machine. We pack her diapers, her rescue medication, her speech-generating device.”

## I. Investigational products (clinical trials)

*“Fortunately, we learned of trial options on the horizon. Once she began the experimental drug, she experienced an immediate increase in seizures, and a few days later, a gradual reduction from baseline activity emerged. To our surprise and delight, her anxiety and ear-piercing vocalizations decreased substantially within the first six weeks. Her gross motor skills also became more fluid and sustained as noted by her physical medicine and rehabilitation doctor around three months after reaching the maintenance dose. For the first time in her life, we attended medical appointments without her wheelchair as she was able to stand and ambulate for longer distances without a need to rest. Expressing her voice more proficiently with her eye gaze communication device has also improved.”*

Though not actually a form of multidisciplinary care, 22% of the polling respondents selected “investigational products in clinical trials.” Again, there were few openings in clinical trials for individuals with CDD to participate in at the time of the EL-PFDD meeting, so its position in the polling standing cannot be interpreted as due to lack of interest. For the sake of the narrative flow, its placement here is fortuitous as it serves as a good introduction for the next discussion topic: What families affected by CDD want from future treatments, and how they will be making treatment decisions.

The highlighted quote, provided by one of the panelists, the mother of a 14-year-old girl, illustrates some of the outcomes which matter most. Even though the trial was an AED, there were improvements

in her daughter's behavior and anxiety, gross motor skills, walking for longer distances, with a significant improvement in her ability to use her eye gaze device to communicate with her loved ones.

Yet, there is a very real risk that that these meaningful benefits might not be among the primary outcomes measured in the clinical trial solely focused on seizure outcomes—which was underscored by the results of the next polling question and subsequent discussion.

## Perspectives on future treatments and considerations in treatment decisions

*“We are in desperate need of disease modifying treatments. Small improvements in our population can make a large impact on the quality of life. Never underestimate the value of small changes.”*

The final polling question focused on what caregivers were looking for in potential drug treatments. Polling participants were asked to rank the top three abilities or symptoms most important for a possible drug treatment to address. There were 46 respondents and 138 responses to the question.

### A. Improved developmental milestones

*“Developing drugs that focus on global brain outcomes beyond seizure reduction is an urgent and unmet need in the CDD community.”*

By far, what caregivers want most are treatments to address developmental delay and allow their children to better reach developmental milestones (this was selected by 76% of the respondents).

In her intro, Utley said treatments need to address the neurocognitive deficits that hinder the development: *“A decrease in apraxia could allow for more control of the body that they are trapped in.”*

This was reiterated by one of the panelists: *“An ideal treatment for my daughter has evolved so much since her initial diagnosis. Five years ago, I would have said seizure control. Do whatever it takes to make these awful, heartbreaking seizures go away. Now, my number one focus would be increased cognition. I truly believe that [she] is in there, that she is stuck inside this little body that will not cooperate.”*

*“Life would be immeasurably better if any or all of these abilities (cortical visual impairment, her fine and gross motor skills deficits, and her profound intellectual disability) could be improved,”* said the panelist who described how hard her family worked on skills acquisition with her baby girl. *“To see [her] make association, to see her understand concepts or be able to signal that she understands who we are, respond to her name or respond to things that are said to her. More complicated cognitive would truly improve her quality of life because it would allow her to interact with a world that may not always be tolerant of kids who are different and who express themselves differently. Her being able to participate more fully in a more typical way would give her more chances to enjoy her life more. If we could somehow unlock the door that keeps her trapped, we would be very, very grateful.”*

### B. Improved language abilities and social communication

*“Improved communication: being able to understand your child's wants, needs, pain, source of discomfort. How that comes, is maybe secondary. If it's spoken language, great. But it may be non-verbal communication. That does overlap potentially with*

*hand use or vision because one of those is likely to be necessary for nonverbal communication. That would really be life-transforming.”*

The second and third choices, receiving 54% and 35% of the respondent’s votes, respectively, both involved communication: improving language abilities and social communication. Any form of communication is welcome, even if it is nonverbal, as it could improve the child’s quality of life.

*“A change in communication abilities could allow a child to inform a parent that a seizure is coming,” Utley said when opening the meeting. “Communication would be huge,” said the father of a 5-year-old girl whose mother spoke on Panel 2. “For her to tell us how she’s feeling, what she needs. She had a ruptured eardrum a week ago, and we found out about it and we felt terrible. It probably happened days prior and we didn’t know about it and that was devastating for us. A small thing like that, that she couldn’t even tell us that her ear was hurting her, but that was very difficult.”*

But parents long for much more: *“Not only for them to be able to communicate to us how they’re feeling in painful moments when we can’t help them and we have to try and figure it out, I want them to be recognized as people and human beings,”* said a mother whose daughter is losing that ability.

During the panel testimony, the mother of the 5-year-old girl spoke about how she had seen a poll circulating on social media that posed the question, *“If you could have a conversation with anyone dead or alive, who would it be?”* Most people chose lost loved ones, influential people or historical figures:

*“The only answer that I could think of was my daughter. I would give just about anything to sit and have a conversation with my girl to really know her. What is her favorite color? Who is her favorite princess? What would she like to be when she grows up? A treatment that would allow her to interact with us, to joke around with her sisters or tell her daddy that she loves him would be worth its weight in gold.”*

### C. Improved walking/motor abilities

*“Movement will give them some inclusion. For my granddaughter simply to be able to have a little more hand control and arm and shoulder control would mean she’d be able to move the wheelchair down the hallway, to the school and not be left behind. Or follow you to the kitchen. It’s not much of a deal. She won’t be walking but she’ll be moving.”*

Close to a third (33%) of the polling respondents selected improved walking and motor abilities as one of the top three priorities for a future therapy, though the mechanism differed.

*“Future therapies focusing on improving bone strength would give her an increased ability to stand and walk with assistance,”* said the caregiver of the ‘almost 14-year-old’ who has undergone hip surgery.

### D. Reduced seizures

*“Treatments for total seizure control would be life-changing.”*

With so much discussion of AEDs and other means of seizure control, it may seem surprising only 30% of respondents ranked seizure control among their top three priorities for future treatments. The lower priority could have been due to the virtually total absence of treatments for the other symptoms of CDD



or because caregivers care more for improvement in downstream impacts than for seizure control. *“Seizing is a part of her life... It’s the other stuff that’s more difficult,”* said a 12-year old girl’s mother.

*“Seizures are not the most harmful aspect of her condition... as on many seizure days, she’s still energetic and playful while she paradoxically spends some seizure free days sleeping or fussing,”* said the mother of the 17-month-old girl who had a very bad experience on one AED. *“So, we are very much looking forward to something that will give not just seizure control but a better quality of life for her.”*

However, others reported that better seizure control improves other outcomes and that seizures and other symptoms are inextricably linked.

*“Ideal treatment would see better seizure control [which] would lead to less damaging side effects on the developing brain and increased neurological function, neuron development and transmission, and brain processing abilities,”* said the mother of the 4-year-old boy on the second panel.

*“I have hope for a day when [she] can use one or maybe two drugs for seizure control that don’t make her agitated, constipated, floppy or sleepy to help her better communicate, to improve her ability to self-feed, toilet, and dress with minimal support, to reduce the burden of severe anxiety and behaviors such as loud and constant vocalizations, self-stimulating and self-abuse are life-changing improvements,”* said the panelist ‘surprised’ by the improvement in other symptoms after her child started an experimental AED in a clinical trial. The point bears repeating because it is critical that the clinical development programs for AEDs to treat CDD-related epilepsy measure the drug’s effects on other CDD outcomes.

## **E. Reduced gastrointestinal symptoms**

“Improvement and bowel motility could allow parents to stop obsessing with the amount and quality of stool.”

Approximately 22% of the respondents selected reduced GI symptoms as one of the top three priorities for future treatment. Aside from the burden of changing diapers on a large child or adult, constipation appeared to cause much discomfort that children struggled to communicate to their families. As one mother said, *“we cannot focus on developing her vision when she’s screaming in pain from constipation.”*

Even a partially effective treatment could make a significant difference in quality of life, according to the caregiver whose daughter’s seizure were becoming cyclical as she approached puberty: *“During the two weeks of seizure activity, [she] is fairly lethargic and has severe bowel cramping on a daily basis. Even a 30% increase in GI motility would help her to recover more quickly and minimize those severe cramps.”*

## **F. Improved hand function/control**

*“Perhaps a treatment could target hand use and assist with self-feeding or give the ability to touch an area to indicate the source of pain.”*

Improved hand function was selected by 20% of polling respondents as one of the goals for therapy—to use hands to assist in non-verbal communication and have the dexterity required for self-feeding.



## G. Improved vision

*“We would love to see more research in therapy directed at visual processing and to identify what she may actually be seeing. Is it double? Is it fragmented? Is it inverted? In a nonverbal child with moderate CVI, understanding how [she] sees is critical to us if she is to make any real progress in her ability to make associations and to learn. Even a 20 to 30% improvement in her functional vision could allow her to make those connections and engage more in the world around her.”*

Approximately 13% prioritized improved vision as one of the top three outcomes, while noting that cortical visual impairment was also critical to using communication devices as well as for eye contact and engagement.

## H. Reduced discomfort

*“We have a long way to go to formulate the best treatments for children with CDD to alleviate pain and give them the chance to experience and enjoy more of life.”*

Ranked next was reduced discomfort, selected by 9% of polling respondents. Discomfort was often associated with other symptoms and health effects associated with CDD.

## I. Improved sleep

*“If we could somehow just figure out a way to help repair the circadian rhythm in these kids to where families could get a decent night's sleep, then you can also face everything else much more fresh and ready for those challenges”*

Selected by two respondents as one of the top three, the discussion on sleep often focused more on burden on the caregiver. However, as already noted elsewhere in the report, at least one panelist said lack of sleep made her son *“very agitated”* and even more susceptible to *“respiratory or GI illnesses.”*

## J. Reduced anxiety

Also selected by two participants, anxiety experienced by individuals with CDD may be under appreciated, but at least one caregiver linked it to the loud vocalizations and behavior in her child.

## K. Other Symptoms

No one chose ‘other.’ However, addressing one condition, hypotonia and/or lack of strength, was frequently mentioned by caregivers, as it often underlies other symptoms.

*“Increased strength and muscle tone will go a long way towards easing the cardio, respiratory, and gastro problems plaguing my brothers and sisters,”* the grandfather said on behalf of his granddaughter.

*“I would like to see improved muscle tone. I see that [she] has intention to answer me, to move her hand on the choice board or her eyes on the eye gaze, but sometimes she has a very hard time because of her hypotonia,”* said the caregiver of a 6-year-old child.

During the discussion, the mother of the 3-year-old boy from Panel 1 stressed that addressing hypotonia could be critical to life-preservation as well as quality of life: *“Improved muscle tone means improved secretion management and improved physical health. That’s the primary, where another [symptom] can sometimes be the secondary, especially if they create life-threatening situations. My husband and I always comment that when [he] has a tonic seizure, he has so much tone in his body. I just wish that we could get that tone for our other times because it would greatly improve the quality of his life.”*

#### L. Targeting the root cause of CDD

*“My hope is that the future will bring advanced treatments that get to the root of his disease, and that this will allow [him] to learn and to be as healthy as possible so that we can enjoy our life together much more than we are currently able.”*

The hypotonia discussion underscored how interconnected many of the CDD symptoms are. Prioritizing any one symptom may lead to missed opportunities:

*“Stopping seizures will not be a cure. This disorder impacts our kids greatly and globally. Please understand that although CDD is certainly neurological in its origin, the impact creates symptoms in many body systems,”* Utley said in her introduction.

The father of a 5-year-old girl offered a similar observation: *“Important drugs to look into more [would be] for communication and vision and motor abilities and not to chase the seizures. The seizures we’ve learned, will come and go and let’s work on some of the other stuff and see what happens.”*

*“As we experience and deal with one symptom, another is not far behind, for every new symptom brings the challenge of how to provide relief and maintain comfort,”* said one mother.

*“We would like things to be meaningful to [him]. Whether that is in choice making, communication, understanding what he wants to play with, something that can develop some meaning for him and his understanding of the world around him. I think that that involves cognition, vision, hearing, the low tone, and the developmental,”* the mother of the 4-year-old boy said during Panel 2.

Ultimately, the solution could be a treatment that addresses the root cause: CDKL5 deficiency.

*“It seems like with every new treatment, there’s a new source of anxiety. What would help us feel more in control? Controlling the seizures, of course, and the GI problems, both the aspiration and the constipation/diarrhea roller coaster, but most of all, I wish we could free her brain from the cognitive impacts of CDKL5,”* said the father on panel 1. *“There’s a sweet, loving, amazing girl just locked in there waiting to get out.”*

As the caregiver said on behalf of his adolescent granddaughter: *“The gene CDKL5 seems to be crucial across multiple domains, which gives me hope that there is light at the end of my tunnel. Where do I place my expectations? Do I choose the road of endless symptomatic treatments like my current drug regimen, or a restart of my dormant CDKL5 gene, or a repair of my active CDKL5 gene? Finally, please see us for our potentials, not our symptoms and limitations.”*

## Post-meeting questionnaire evaluating CDD caregiver perspectives on clinical trial participation and the benefit-risk analysis of future treatments

One purpose of an EL-PFDD meeting is to not only assess unmet needs and determine which clinical outcomes matter most to a community affected by a particular disease or condition, but also to learn how they make decisions about treatment. What would they be willing or unwilling to accept in terms of route and convenience of treatment administration, or potential side effects obtain their desired outcome? Might there be risks unique to their condition that they would be more averse to? Every disease community is different. Caregivers of children who have a disease with a high mortality rate might do almost anything for a treatment to extend the child's life. Adults with a neurodegenerative disease may be willing to take a medication that increases their risk of heart disease if it prevents further losses.

At one point in her testimony, the mother of a 17-month-old girl, who had had a potentially life-threatening adverse event on treatment shortly before the meeting, described her own reappraisal of the benefits and risks of treatment decisions for her daughter: *"We would like for her to function at the highest level possible from a visual, motor and intellectual point of view and have the fewest possible seizures, but only if this does not affect life-sustaining functions,"* she said.

However, with so much to share at the meeting about the disorder as well as the inadequacy of the existing treatments, there was little time to explore how families affected by CDD might weigh benefits and risks in their treatment decisions. Nevertheless, community feedback on benefit-risk is essential both for members of industry deciding whether to pursue development plans for some treatment options and how to design their clinical trials, and to FDA reviewers considering new drug applications.

Thus, the two patient advocacy organizations representing the CDD community that hosted the meeting felt that there was a need for more data. They decided to conduct a short post-meeting survey with additional questions to better understand what risks associated with a new treatment would the caregivers of an individual with CDD contemplate or accept in exchange for the treatment outcomes (or benefits) that would be most important to their child and family.

The questionnaire briefly touched on some of the same topics as the live polling to provide context to participants response about their benefit-risk calculations if presented with a hypothetical treatment that was partially effective, or very effective. Most of the questions were open-ended and, in some cases, presented the participants with unpleasant scenarios that, nonetheless, reflect real work benefit-risk choices that patients and parents of children with life-limiting diseases sometimes must make. (The survey questions and complete responses are shown in Appendix #).

### Characteristics of the individuals with CDD represented in the survey:

The questionnaire was posted online as a Google document, and notifications were sent out by the patient organizations to the CDD community in the United States and internationally. Participants were given three weeks to post their response. There were 36 non-duplicate responses. Of note, most of the

respondents (72%) did not attend the meeting—and approximately 61% of the overall respondents did not watch the webcast live or had not watched it yet.

Consequently, many the questionnaire participants did not participate in the live polling of the meetings. However, the distribution of ages was similar to that of the live poll (those who participated in the live poll may have been slightly younger—two individuals with CDD represented in the questionnaire responses were in their 30's, and there were fewer infants represented).

**Symptoms:** The symptoms that mattered most were also quite similar between live polling and questionnaire responses. However, as the question was open ended, participants were able to list some complications not mentioned during the meeting. For instance, a caregiver of the 35-year-old woman prioritized *“central sleep apnea”* along with *“drug resistant seizures”* as the symptoms that mattered most—possibly because the “unpredictable apnea episodes” meant that she *“requires 24/7 care.”* Some symptoms were mentioned more often. For instance, four caregivers raised the issue of anxiety—one listed *“anxiety/hyperventilating”* as one of the top three symptoms in their 11-year-old girl. Others described aspects of the symptoms in a particularly compelling or moving way.

One caregiver who watched the webcast but could not attend the meeting explained how hard to travel with her 12-year-old son: *“As he gets bigger, we leave the house less and less because it’s too difficult and or there are not public places that have appropriate changing areas for anyone larger than a baby.”* While another caregiver representing a 12-year-old daughter wrote that GI issues, which this adolescent girl included *“gastrointestinal gas, rectal prolapse and chronic constipation... impact everyday living by limiting movement and daily activities, causing pain and discomfort.”*

The caregiver of a 4-year-old girl who *“has the same developmental and cognitive functions now as she did at 3 months old”* could not limit the symptoms that mattered most to just three and listed hand movement as the fourth: *“It’s like she doesn’t have hands. If she could grasp and support herself, she could be sitting/playing independently which we very much want [for] her.”*

The caregiver of a two-year old boy also highlighted a motor issue, *“no head control,”* as contributing to developmental delay: *“If he could sit better, he could be motivated to see more. If he could be motivated to see more, he would be motivated to interact with his world more, and others would be more motivated to interact with him as well.”*

One marked difference from the live meeting was the inclusion of a handful of individuals whose CDD appeared to be less severe. One, the caregiver of one 21-year old young woman characterized their daughter’s condition as *“unique.”* For instance:

- Her epilepsy: *“During the first 13 years of her life, our daughter had at least one nocturnal tonic-clonic seizure each week. This has improved dramatically as she has not had a tonic-clonic seizure in over 8 years and rarely has absence seizures (a couple each year).”*
- Her developmental delay: *“Our daughter functions at a high level compared to most CDD diagnosed children but is unable to do most basic tasks (hygiene, food preparation, etc.) and requires 24/7 care. She continues to learn, and her abilities continue to slowly improve with time and repetition.”*
- Her physical development issues, *“our daughter has a poor gait and kyphosis. These have hampered her ability to easily move but she can walk significant distances (a couple miles). These continue to worsen with time, but we continue exercise on a daily basis.”*

The milder clinical presentation in some had bearing on their caregiver's benefit-risk analyses regarding experimental therapies (as described later)—though not always in the way one might predict.

Another caregiver described an 11-year-old girl atypical in another way because *“her first documented seizure did not occur until she was 8”* years old. While this could have been an unusually long ‘honeymoon period,’ it was now over, as she has worsening seizures, and *“respiratory issues due to aspiration.”* The caregiver also described another way sleep issues could be dangerous in an unattended child. *“She hurts herself at night if someone’s not there to stop her. She scraped her entire foot on the wall all night long without making a sound. We didn’t realize it until we saw the dried blood on the wall.”*

The caregiver stressed one chief problem with the drug treatments used to combat CDD: *“It’s so hard to pinpoint what is causing her sleep, lung, and other issues—whether it’s her brain or her medications.”*

**The effectiveness and shortcomings of current treatment:** To provide context to the responses about future treatments, the questionnaire also asked about participants experience with current treatments and therapies.

The treatments and therapies were similar to what was described during the meeting, though the survey responses added details that perhaps were missing from the facilitated discussion. For instance, several made reference to mobility equipment and orthotics support: *“We have lots of equipment (supportive chairs, stander, wheelchair, bath, pulmonary equipment, feeding tube equipment),”* wrote one caregiver and another mentioned a *“bilateral ankle foot orthotic..., stander and gait trainer.”* A couple acknowledged the use of *“CBD oil”* or *“state CBD product.”* There was also confirmation of the challenges accessing assistance communication equipment mentioned at the meeting: *“Too poor to use Tobii [an advanced eye control and tracking system], attempted the Podd system [a more basic platform] but still unable to use accurately with her,”* the caregiver to a 4-year old girl wrote.

During the live polling at the meeting, the participants had been asked to use a modified CaGIC scale to explain how well their treatments did or did not improve quality of life—a difficult question given the mixture of symptoms and chronic conditions that develop in an individual with CDD and the lack of any treatment that addresses the disorder in its entirety. About 16% reported that treatments had substantially improved quality of life, with an occasional mention of the improvements due to diet or of an effective AED (for the time being), though there were few tales of durable treatment benefits.

The survey responses differed. Although the questionnaire did not repeat the CaGIC scale question, the open-ended format provided the opportunity for participants to characterize the shortcomings of treatment. Consequently, there were some detailed reports of moderately and substantially improved quality of life in some individuals, perhaps because the severity of the disorder was less at baseline.

For instance, one caregiver reported their 6-year-old girl whose epilepsy had *“completely stabilized”* for a couple years on *“Keppra, Sabril, Ketodiet.”* Notably, she can also *“walk, talk a little bit and is autonome in a lot of things. She is interested in a lot of things and is developing quite well over time. She is social, has little friends.”* Similarly, the caregiver of another 6-year-old girl wrote that she *“is okay, has only a few paroxysm”* on *“levetiracetam [Keppra] and Orifiril [Valproic acid].”*

*“Her current symptoms are well managed with her treatments,”* wrote the caregiver of the 21-year-old young woman with a milder clinical presentation than most. Another caregiver reported that her 12-year-old’s epilepsy had improved, *even “without medication.”*

Others reported improvements (for the time being). A caregiver to a 1-year-old wrote: *“She has better seizure control and physical abilities have improved during [the] current treatment regimen (Keto diet, Keppra, Vitamin D, Poly Citra K, PT/OT). All symptoms have improved in some capacity. Seizures went from five to eight a day to now averaging one per week. Vision has gone from zero focus to sustaining a gaze up to fifteen seconds on objects and faces. Motor skills: Learned to roll both ways. Head control has improved [and [she is] able to sit with assistance for [a] long period of time.”*

While not reporting marked improvement, other caregivers seem to have made a sort of peace with the amount of seizure control that they currently have: *“We don’t try for seizure freedom. As long it’s only a couple a week,”* wrote the caregiver of a 3-year-old girl; while the caregiver of a 23-year-old young woman reported, *“We have decided the seizures are as stable as [we] will ever get them and have stopped trying to get our daughter seizure-free. Constipation, we deal with prescription drugs, and crying spells are dealt with by home comforts, music, sensory lights, and some pain management.”*

However, most questionnaire respondents shared stories of limited or no benefit from currently available treatments. As described by the caregiver of a 16-year-old girl: *“the medicines are ineffective, the therapies are beneficial. The time consumed by daily care is the biggest downside.”*

Some treatments improve one aspect of CDD, only to worsen others: *“Anticonvulsants are the major problem, almost all of them had a different side effect in our daughter.”* Many spoke to how *“all the drugs that we give her are sedating”* causing *“confusion,”* or *“dulling personality.”*

*“She’s been on at least 14 different AEDs in her life. No impact,”* wrote the caregiver of a 9-year-old girl. *“Nothing we have done improves her quality of life with the exception of the ketogenic diet. No therapy or meds help her function better be it eating or getting around for herself. It’s disheartening.”*

The caregiver to a 4-year-old girl on jejunal feeds of total parenteral nutrition (TPN) reported the child had gained 10 pounds but that her GI symptoms had worsened, and that due to the port, she now *“has a risk of a central line infection.”* In addition, *“seizure medications have never done anything. The VNS has helped some, however, she still has seizures all the time. There is nothing that has been able to assist us successfully with communication and I am a speech-language pathologist (SLP), so it really is sad.”*

The caregiver of the 12-year-old girl with GI issues reported that, where they reside, access to PT/OT is *“rarely available. We haven’t found a treatment for excessive intestinal gas; we have tried all treatments available without meaningful success. Using a lactose-free diet is very limiting as products are few. Her seizures are daily, so we do not have seizure control. Side effects of multiple drugs simultaneously have caused her cognitive delay. Her gums and teeth are in a fearful state. Some AEDs get her very agitated, some lethargic... some have caused loss of muscle control, fuzziness, dizziness, etc.”*

For many, the treatments simply do not work well. Despite treatments, one caregiver reported their 9-year-old child requires *“24 hours intensive care at home, [and has 10] seizures a day.”*

The caregiver of a 4-year-old girl wrote, *“We are effectively stagnant. There seem to be no improvement to her developmental delay/hand movement. Her seizures seem to exist outside of how we treat her.”*



*They beat to their own drum and nothing seems to help. The biggest downside is that we spend so much time making her bottles and preparing her supplements for Keto and it doesn't seem to help]."*

*"My daughter has been on medication since she was twenty days old; it is frustrating never to see an improvement,"* wrote the caregiver of a 2.2-year-old girl; while the caregiver of a 12-year old boy reported: *"Nothing has ever been 100%. We are only treating symptoms—not the problem."*

These responses are important when considering survey participant perspectives on the risks of experimental therapies—but risk must also first be weighed considering what is wanted from treatment.

**Goals for future treatments:** One of first questionnaire responses provided a synopsis of the most common goals of treatment among the survey participants: *"Improvement of mental status, enabling verbal communication and stopping seizures."* A thematic review found that a similar proportion wanted treatments to better control epilepsy, address global developmental delay/neurocognitive issues and increase verbal/non-verbal communication—though communication was mentioned most:

- *"Something that would allow for communication and greater developmental growth. I could deal with the seizures if we could treat the rest of it."*
- *"To not be able to communicate with our daughter is difficult and devastating."*
- *"If there would exist something to activate speech more, we would be happy."*
- *"Would love for her to become more social. If she could communicate with us that would be great!"*
- *"We wish she could tell us what is hurting her or bothering her and what she would like us to do to aid in her comfort."*
- *"I'd like her to be able to communicate. We have no idea how she feels or what she needs! It's been a 9-year guessing game."*
- *"What I would give to find out the reason why my daughter [is] going [through] spells of crying for days at a time."*

Communication was associated with neurocognitive abilities: *"I would love for my child to engage with me... communicate basic needs and attend to her surroundings,"* wrote one caregiver. Another asked for treatments that would help their daughter *"be a functioning member of society. I could handle the seizures if she were able to develop skills, meet basic milestones and be an active member of our family."*

*"Treatments to help with fine and gross motor skills,"* was the next most common goal of therapy: to *"be able to stand, take a few steps," "gain ability in use of hands," and for "purposeful hand movements."*

An overlapping goal, improving the ability to perform daily living activities (and decrease dependence on caregivers), was also commonly mentioned: *"Improved motor planning so she is better able to participate in activities of daily living (such as self-feeding, dressing, toileting. Being able to pull her pants up/down would be a huge help, even if she still needed assistance with peri-care,"* wrote one caregiver.

Several listed increasing muscle tone and strength—again linking hypotonia with respiratory function.

*"Improved muscle tone and control would be the best treatment as it would improve overall quality of life,"* wrote one caregiver. Better quality of life as a goal of treatment was also frequently mentioned:

- *"Quality of life over quantity of life!"*



- *“We are looking to improve her quality of life. For our daughter, seizures are paramount to improving that and by eliminating them, we have better prospects for reaching other goals.”*
- *“We want a better quality of life for her. Sometimes, I think we haven’t seen her real personality due to the seizures, her medications, and the pain she must feel.”*

GI and feeding issues were also prioritized: “Reflux/constipation control would be a worthy trial,” one suggested. *“Better management of the GI problems. I am 100% certain that intestinal gas triggers seizures. If we could get the gas under control, I believe it would have a positive impact on her seizure management also,”* the caregiver of the daughter with severe GI issues wrote.

Even a caregiver relatively satisfied with the effectiveness of current treatments wrote they would be *“happy...if there would exist something like a ketopill,”* in other words, something that could achieve the benefits of the ketogenic diet without all the effort. Many other responses also focused on improving upon the existing treatments for seizure, with more than one caregiver looking for a “medication that would control seizures without impacting motor and visual abilities.”

Other treatment needs mentioned were *“increased eye contact”* and *“vision and hearing,”* linked to neurological processing, *“reducing anxiety and behaviors [suspected to] stem from lack of communication,”* improved sleep quality, and reduced pain. In addition, caregivers of some of the adults with CDD were concerned with life preservation and prevention of loss: *“We would like to see an elimination of any losses (Parkinson’s-like symptoms can occur with increased age),”* one wrote.

Finally, several called for a treatment to address the root cause of CDD—rather than symptomatic treatments. *“More time and money put into treating the problem, NOT the symptoms of it!”* wrote one caregiver, and another: *“I do not trust that seizures will be controlled without a disease-modifying treatment so I am much more skeptical and critical of enrollment in trials that only address this aspect.”*

### **What risks would be considered to obtain the desired benefits of a potential**

**treatment:** The questionnaire posed two questions on CDD caregivers’ benefit-risk analyses: 1) What side effects they would be willing to tolerate in a potential new treatment addressing the symptoms that mattered most?<sup>6</sup> And: 2) What would they be willing to risk for a treatment that had a major impact on CDD’s root cause (and the health challenges it causes). Some of the hypothetical side effects mentioned were quite severe, ranging from carrying a risk of life-threatening reaction to comorbidities that could complicate care or lead to end-organ disease decades later in life.

Participants offered a wide range of responses that, to some extent, reflected differences in the spectrum of CDD, the severity of symptoms and the response to currently available treatments. Caregivers also expressed a healthy dose of skepticism about the potential effectiveness of treatments.

One caregiver, the speech language pathologist, thought it misleading, or worse, to suggest there could be a treatment targeting the root cause of the disorder, CDKL5 deficiency: *“I think there needs to be research for a potential cure, but when a gene like CDKL5 is impacted in such a way to cause the severity*

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<sup>6</sup> These included common side effects such as nausea, vomiting, loss of appetite, weight gain, headaches, back pain, fatigue, increased risks infections as a result of treatment, a small risk of a severe life-threatening reaction or serious side effects to the heart, liver, or kidney that may affect normal organ functioning and require immediate medical attention or a treatment that may result in possible serious comorbidities such as cardiovascular disease, kidney disease, diabetes, and weight gain for the rest of their lives.

*it does to some of our children, it cannot be treated as if a cure is on the horizon. A cure is NOT going to make our current 4-year-old typical ever, and I feel it a disservice to insinuate such a potential.”*

Indeed, it was not the intention to imply that any treatment under evaluation could restore an individual with CDD to the health and state of development they might have had without the disorder. But a treatment that redresses the underlying genetic disorder might markedly decrease seizures and allow neurologic development that over time could lead gradual improvements in tone, motor function, cortical visual function and the ability to communicate. It might alleviate chronic pain of which the caregiver is not even aware. There are other genetic deficiencies that are being treated leading to dramatic improvements in outcomes such as survival in other rare diseases. These treatments usually win approval based on preliminary data. While some have known side effects such as liver toxicity that requires close monitoring or have an uncomfortable route of administration—it is difficult to anticipate the potential side effects over the long term based on short studies in very small numbers of children. Would caregivers accept such risks?

Others may have little hope in potential of treatment, based at least partly upon their experience with AEDs. As discussed at the EL-PFDD meeting, the large number of AEDs now available do not have much effect on the non-epilepsy-related symptoms of CDD; and the community has expressed collective disappointment in their limited benefits, and dismay when the drugs have the opposite of their desired reaction or untoward side effects that a child or individual with CDD may not be able to communicate.

*“When introducing new AEDs, the trial and error approach is slow and bothersome as she cannot tell us how she is feeling. Getting up to an effective dose can often take weeks and there are almost always unwanted side effects before her body adjusts to the new chemicals. Sometimes we end up spending weeks torturing her with a new drug that ultimately doesn’t work for her or suit her, just to wean it right back off again,”* wrote the caregiver of the girl with severe GI issues, who, along with several others, wrote about the risks they would consider before even reaching the questions on risk-benefit, with some expressing greater aversion to risk:

- *“The biggest factor to consider about using treatments for us is side effects of medications and interactions with current treatments.”*
- *“[A] moderate level of risk would be tolerated for treatment.”*
- *“When making a decision on a therapy or treatment, I look for the least amount of side effects.”*

There was a similar range of responses to the benefit-risk questions.

### **Some caregivers are not willing to take any risks in children with relatively stable health:**

On one end of the spectrum, several participants indicated they would not accept any risks of severe side effects whatsoever for an effective symptomatic treatment in their child, and would not consider the risk of life-limiting events in exchange for a major global improvement addressing the root cause of the disease, with short answers such as *“none”* and *“nothing”*, *“no risk”* and *“I don’t know,”* while another responded, *“I am not prepared to accept any of those side effects except a little weight gain.”*

*“In consideration of the aspect that she is actually more or less stable, we wouldn’t go for additional risks,”* wrote the caregiver whose daughter’s seizures have improved but still has some paroxysms.

The caregiver whose 21-year-old daughter only had a couple of absence seizures a year for the last eight years provided an explanation for a similar response: *“Our situation is somewhat unique due to our*

*daughter's overall good health and quality of life. We are not willing to take any risks that could result in risk of life or comorbidities occurring."*

These responses are entirely understandable while current treatments are controlling major symptoms and the child or loved one is doing well—to use one idiom, ‘why throw a spanner in the works?’

Other caregivers had concerns, perhaps unique to developmental disorders, about exposing children to treatment-associated risks to make them conform to others with more typical development. What side effects would they risk? *"Nothing at all,"* wrote a caregiver of a 6-year-old girl who is doing well on current treatments. *"We have a perfect treatment for our girl and aren't willing to change anything. She has her deficits and her problems but is doing quite well. She develops well, is a happy, social girl, interested in a lot of things. We don't want to risk all this for a trial. We accept her as she is. She is stabilized in epilepsy. For us, she is just perfect as she is."*

*"Not sure what risks I would take because I do accept her for who she is,"* wrote one whose 11-year old daughter had a good response on Epidiolex who then added that it was *"hard to answer at this time"* what they would risk for a treatment leading to an overall improvement in the major symptoms of CDD.

The speech language pathologist had a particularly passionate reaction: *"I will never allow her to be a full-fledged guinea pig and participate in a trial with unknown side effects that could lead to death."*

**Manageable routine side effects are acceptable as long as there is no decreased quality of life or increased suffering:** While the language pathologist was not interested in treatments that might harm major organs, they wrote *"small side effects [that] do not pose a significant negative impact on quality of life can be dealt with, that [make] the benefit of no seizures worth it, [would be] doable. Comorbidities are also out as well/unless we are talking a significantly improved quality of life. If you said there was a drug that could cure all CDKL5, BUT the tradeoff would be a shortened life, I would take that trade. BUT it would have to be a guarantee that she wouldn't suffer at all."*

*"We would not risk side effects that noticeably reduced her quality of life below baseline, caused serious comorbidities, or impacted longevity,"* wrote another caregiver.

*"Fatigue, weight gain, possible effects on organs,"* wrote the caregiver to the oldest individual in the survey, a woman aged 35 years. The caregiver added, *"At this stage of her life neurocognitive development is not as important as it once was. Lifespan and quality of life is more important."*

*"We have always prioritized quality of life over quantity of life in treatment considerations. However, risks that might cause undue suffering would be weighed heavily,"* wrote a caregiver who wants to see an increase of their adolescent's ability to participate in the activities of daily living but also added, *"Our risk consideration might depend on the current state of her health when the study option presented."*

*"Nothing associated with pain"* wrote one caregiver, while the caregiver to the non-verbal 25-year-old responded: *"She must be comfortable."*

**Pain or suffering are a particularly important factor to consider when a child cannot tell you about it:** As the previous comment suggests, the risk of pain is viewed differently by caregivers when the child may not be able to communicate if something is causing them stress or discomfort.

*"[She] is non-verbal and we must make all decisions for her. I am not willing for her to be in any kind of pain in exchange for less seizures. We have lived through some very rough times where [she] moaned for hours on end,"* wrote the caregiver of a 30-year-old woman. Even so, this caregiver would consider a small risk of death in exchange for significant improvement in neurocognitive development or the ability to communicate—as she had already *"lived well beyond what we were told her life expectancy was."*

*"I certainly am not cool with major safety risks of treatments. If it TRULY helped him build strength so that he could hold his head up or avoid severe respiratory infections I would consider some other risks. Parents already struggle making daily decisions for our kids that can't communicate,"* wrote the caregiver of a 2-year-old boy.

*"Less is sometimes more! I wouldn't want to experiment too much with her. Anything that brings her pain or takes away her personality I wouldn't want to try,"* wrote a caregiver to a 3-year-old with inconsolable crying. *"Eating... she does really well, [so] side effects like nausea or vomiting are a no go! If there was a med which could help her communicate with us, maybe I would risk some side effects listed."*

*"If it worked, she would be able to communicate to me how [side effects] were affecting her daily life and she could have a say in treatment. Right now, the drugs we give her list all these side effects, but I have no idea if she is experiencing them,"* wrote the caregiver of a girl whose current treatments are *"not [working] very well."* Consequently, the caregiver *"would be open to the 'common' rather benign side effects. Any risk greater would need to be considered on a one-on-one- basis with her doctors."* As for an unknown risk of death that might come with a global treatment, *"Yes,"* this caregiver wrote. *"I would consider it. Without concrete data in front of me it is difficult to say if we would do it, but we would at least consider it. My child is pretty significantly affected by CDKL5 and her lifespan is not guaranteed."*

**Caregivers will apply the same criteria to trying potential new treatments as they now apply to existing treatments with side effects:** *"The side effects are similar, if not the same, [as those of] the drugs that CDD children and adults currently take just to manage their symptoms with minimal if any change in the symptoms whether seizures, sleep, [or] GI issues. Seizures are difficult to deal with but the possibility of gaining basic life functions that many CDD children live without is far more valuable. To give our children that possibility in life? Yes, we are willing to take those same risks,"* though the caregiver added that *"death would be a risk we would not be comfortable taking."*

According to the caregiver whose child did not have a seizure until she was 8 years old: *"We've discovered that every treatment seems to have a significant side effect. Every new therapy, medication, and treatment, we take into consideration her health at that point in time. If her GI issues are manageable, we take a risk by giving a medication that increases GI problems, if it will help her more problematic seizure control. We take each option and weigh the benefits and consequences depending on how she's doing on that day. Yes... I would trade a few years of her life or take that very small risk of death if it means a cure or a very large improvement in her quality of life. We're already taking risks by giving her medications that can significantly—and probably do affect her lifespan negatively."*

*"The seizure meds she's been on have pretty bad potential side effects and yet she still takes them. Potentially life threatening or comorbidities would give me serious pause. If the treatment is worse than the disease, that's a no for me,"* wrote the caregiver to a 9-year-old girl whose quality of life has not been improved by any treatment other than the ketogenic diet.

**Many respondents suggested that they would be willing to consider common side effects—as long as they didn’t outweigh the benefits of treatment:** Several caregivers mentioned common side effects such as *“loss of appetite, weight gain, fatigue,”* and *“temporarily side effects.”*

- *“The common side effects such as nausea, dizziness, loss of appetite if they were temporary.”*
- *“Nausea, vomiting, diarrhea, small risk of life-threatening disease.”*

*“Facing her condition nowadays, common side effects do not look a problem; weight gain would be a plus for her, in fact. Maybe risk of kidney disease or cardiac arrhythmias leading to sudden death would be of concern to us,”* wrote the caregiver of a 3-year-old girl with dysphagia and respiratory conditions.

Caregivers of children who are very ill or whose life is in jeopardy due to CDD will accept a high level of risk: *“To be honest, unless a treatment is developed that improves my son’s neurological health, I believe his life will be considerably shortened. I would be willing to take considerable risk for an improvement,”* wrote the caregiver of a boy 3 and a half years old. *“If my son doesn’t get a treatment for CDD he will likely die prematurely. I would be willing to take considerable risk.”*

*“I would be willing to take some risk since I’m afraid I’m losing my son already,”* wrote the caregiver of another 3-year-old whose son has constant respiratory issues and has spent weeks in the hospital. *“I would be willing to risk those things, since I’m not sure how long my son will continue to live.”*

*“We would probably accept a high level of risk in order to improve our daughter’s condition in hopes of finding a cure,”* the caregiver to a 16-year-old girl whose current *“medicines are ineffective.”*

*“We are willing to risk no reduction in seizures for improvement in other symptoms, kidney and liver effects, slow weight gain and growth, fatigue, skin irritations/eczema, frequent doctor visits and blood draws,”* wrote the caregiver for a 4-year-old boy whose family wants more options.

**Most but not all CDD caregivers would accept some risk of death to access a partially effective treatment for the global symptoms:** Some responses to the second question about a risk of death or shortened lifespan in later adult years were mentioned above. Looked at separately, many reported they would be willing to accept such risks if the treatment appeared at least partially effective:

- *“Yes, we would consider all of these risks. We would be willing to give him a better life, that may be shorter due to treatment risks.”*
- *“In case of improving all the symptoms, enabling communication skills, I will accept treatment with a very small risk of death.”*
- *“Yes, no doubt, we are willing to take this risk.”*
- *“Yes, yes and yes. But good safety profile would need to be established in preclinical questions and other diseases in clinic with similar approach (for example, gene therapy).”*
- [Would consider] *“possibilities of developing future comorbidities, for example, a small risk for developing contractures or certain types of cancer.”*
- *“If the treatment was really that promising, I would risk crazy things happening as long as the risk was VERY SMALL.”*

A comparison was made to surgery: *“Considering all surgery carries a small risk of death, that probably is unavoidable. If a treatment would considerably cure her problems, help with her cognition and*



*development, and improve her quality of life, I would probably consider it even if it meant shortening of her life span in her later years. I would not consider anything with a risk of incapacitating her further."*

*"A shorter life span bothers me less than a lifetime like she is now,"* wrote the caregiver to a 9-year old girl fed by g-tube and virtually no fine motor and limited gross motor skills.

*"Yes—we would be willing to try a treatment to improve cognitive development and communication with a very small risk of death,"* caregiver to a 16-year-old girl, who added. *"We feel the focus should be on gene, enzyme and protein therapies in order to cure the condition."*

*"Yes, If there ever was a treatment like that, I would risk shortening her lifespan. I would love to get to know her and for her to enjoy life even if it means a shorter life,"* wrote the 3-year-old girl's caregiver.

Some were torn: *"I think it is unfair that we are even faced with such questions. What other parent has to weigh these things?"* wrote the caregiver to a 4-year-old girl with no improvement to her developmental delay and hand movement. *"To risk shortening her life for more function I would say yes but that seems like playing god to some extent. We know how lucky we are to have her with us when so many families have lost children. At the same time, it seems selfish to not want more for her."*

*"We would consider a treatment that significantly improved neurocognitive [development] or the ability to communicate if there was a very small risk of death. We would probably not consider a treatment that shortened lifespan and instead wait in hope that a better treatment was developed later without affecting lifespan,"* wrote the caregiver who quit a job as a research coordinator to care for their child.

*"I am not willing to take even a small risk of death for treatment,"* wrote the caregiver to a 1-year-old girl who seemed to be having some progress at the time of the survey. Nevertheless, the caregiver added, *"I would however consider treatment that has a risk of shortening her lifespan in adult years."*

Others indicated they were *"not willing to take a risk that will shorten her life or lead to death,"* and *"not willing to try it if death as a risk is involved."*

### **The question might be easier to answer if there was a potential treatment on the horizon:**

Some caregivers wrote they might answer differently, if there was a clinical candidate to choose:

- *"What a difficult question to answer—especially with no short-term promise of a drug that will seriously improve our kids."*
- *"I would be inclined to think more deeply about an answer if I had a narrowed-down list of terrible hypotheticals."*
- *"Of course, all would like to avoid serious permanent side effects. Risk of short-term side effects more acceptable if [there was a] chance of a real "cure", i.e. disease-modifying treatment."*

Finally, as the caregiver to a 23-year-old woman wrote *"I can't answer that question until it is giv[en] to me. I would have [to] weigh up the options as [to how] will the 'cure' affect my daughter worse than the symptom it's supposed to be treating. My daughter is a healthy girl so I wouldn't be sacrificing damage to other parts of her body i.e. heart, kidneys, liver, but I would probably take slight side effects if it improved the symptom."*

### **Perspectives on clinical trials**

To develop future treatments, participation in clinical trials will be required—so an open-ended question asked about whether caregivers had ever entered their child into a trial, what had been their experience, and would they consider entering one in the future. The survey also asked a multiple-choice question about factors that would influence their decision to participate in a clinical trial (see Figure 1).

A third of the respondents (n=12) reported that their child had participated in clinical trials, the remainder had not. The experiences of those who had was mixed. About a third reported good experiences on the trial medication, if perhaps temporary, another third described the process but didn't mention the experience on the study drug (had not started or noticed a response yet), while the remainder either did not benefit or had adverse reactions. Most said they would consider entering another study, though a few would be more cautious. In the additional comments section, a number suggested that they were waiting for better therapeutic options—namely those addressing the underlying cause of the disease. The following responses are roughly in the order of positive to negative:

- *“Epidiolex at NYU—best decision/ treatment we have had thus far.” [Notably, this was a caregiver who was not certain they would consider other risks for treatment at this time.]*
- *“My child participated in an open label phase 2 study and continues to be in the extension phase of the study. I don't have to travel far, and the benefits of the study have outweighed the burden of participation.”*
- *“It worked well for 2-3 years and slowly the seizure activity crept back up. I would try another... depending.”*
- *“Yes – ganaxolone; Slight improvement in seizure and GI symptoms without too much additional downside. Some additional doctor appointments as well as documentation.” This caregiver stressed: “We feel the focus should be on gene, enzyme and protein therapies in order to cure the condition.”*
- *“Yes, on the Marigold [ganaxolone] Treatment. Was smooth but definitely a commitment.”*
- *“Yes. Good experience, great PI and trial site. Protocol not burdensome.” This caregiver added: “What we are waiting for is disease-modifying treatments that can really address the underlying disease so we can have improved quality of life for our child including basic communication and social interaction. Not just better epilepsy drugs.”*
- *“We have just begun the process of enrolling in the Arcade [TAK-935] trial. We have had only one study visit and have not begun the drug. I would consider entering a clinical trial if the benefit outweighed the risk.”*
- *“Yes, we are in the Marigold [ganaxolone] study in the double-blind portion. We have not benefitted much from it at this point.” They added, “We are desperate for something at this point!”*
- *“My daughter participated in the Epidiolex (cannabidiol) trial back in 2016 and [it] did not work. No seizure improvement was noted. However, no negative side-effects, either. Yes, I would enroll on a clinical trial that would improve symptoms if given the opportunity.”*
- *“Yes. We participated in the ganaxalone trial. Sadly, the drug had adverse effects for our daughter; however, it was a good experience and we contributed to research so not a total failure. We would absolutely try another trial again in the future.”*
- *“She has. We would consider it again, but cautiously. The drug in question did not end up working for her once we bridged into open label. So, for us, it ended up being a waste of time where [she was] on placebo for the blinded portion. It was definitely a learning experience, but I will think twice before doing it again.”*
- *“Vigabatrin trial to control seizures. Initial adverse reaction with increased seizures on too high dose. Not sure I'd put her through another trial.”*



For the majority who have not been in clinical trials, most would consider entering a clinical trial though, as indicated by the responses to the benefit-risk analysis questions, there is a solid block of participants who are extremely reluctant or even firmly opposed to entering a trial:

- *“I don’t think we would be up to it.”*
- *“We don’t want that our girl is considered as someone you can use for a trial.”*

The speech language pathologist expressed reluctance: *“We have considered but ultimately the potential was not worth the small chance it might help. We have tried enough medications and failed to not feel it necessary to play this game when other children with CDKL5 have not all sung its praises... While I am all for eradicating the impact of CDKL5, that is not possible currently. I appreciate the need to help other children in the future, but the selfish mom in me says, if it isn't going to help our daughter now, and in her lifetime, I do not feel the need to subject her to a series of trials that might wreak unnecessary and irrevocable damage.”*

Others indicated their decision would depend on the drug and their child’s need at the time:

- *“Depending on the possible outcomes to improve her life, we may want to participate in the future.”*
- *“Not yet. I would if there is a promising trial at a time we need to consider a new drug.”*
- *“Yes, but I would have to know more about a trial before entering her into one. We would consider enrolling in a trial depending on potential effects. Symptomatic treatment while good for short term is not what I would look for as this is a global disease and requires global treatment.”*

About a quarter of the respondents had tried or wanted to participate in clinical trials but ran into access issues such as exclusion criteria—including older age—or the lack of trials abroad:

- *“Tried to get into Epidiolex. But they were only taking Dravet kids.”*
- *“As [she] is an adult, she has not been eligible for a clinical trial. Please, please include older people living with CDD in clinical trials.”*
- *“She hasn’t been part of a trial because there hasn’t been one near enough for us to access.”*
- *“I would rather participate, if treatment can be performed in Brazil.”*
- *“No. We did not because we live outside the US and the travel requirements were too onerous and there was a 50% chance we [would be] given placebo.”*

One caregiver wrote because of numerous factors could not get into a trial, and now the window of opportunity seems to have passed: *“I tried to get her in a trial near our home”* [but she had started a medication that temporarily excluded her from the trial. *“When I found out they were now accepting patients on that drug, I contacted them back, but they did not know the change had been approved.”* Month later, they told the family they could accept the girl, but she was *“having numerous respiratory issues so we decided that giving her a trial medication is not in her best interest at this point.”*

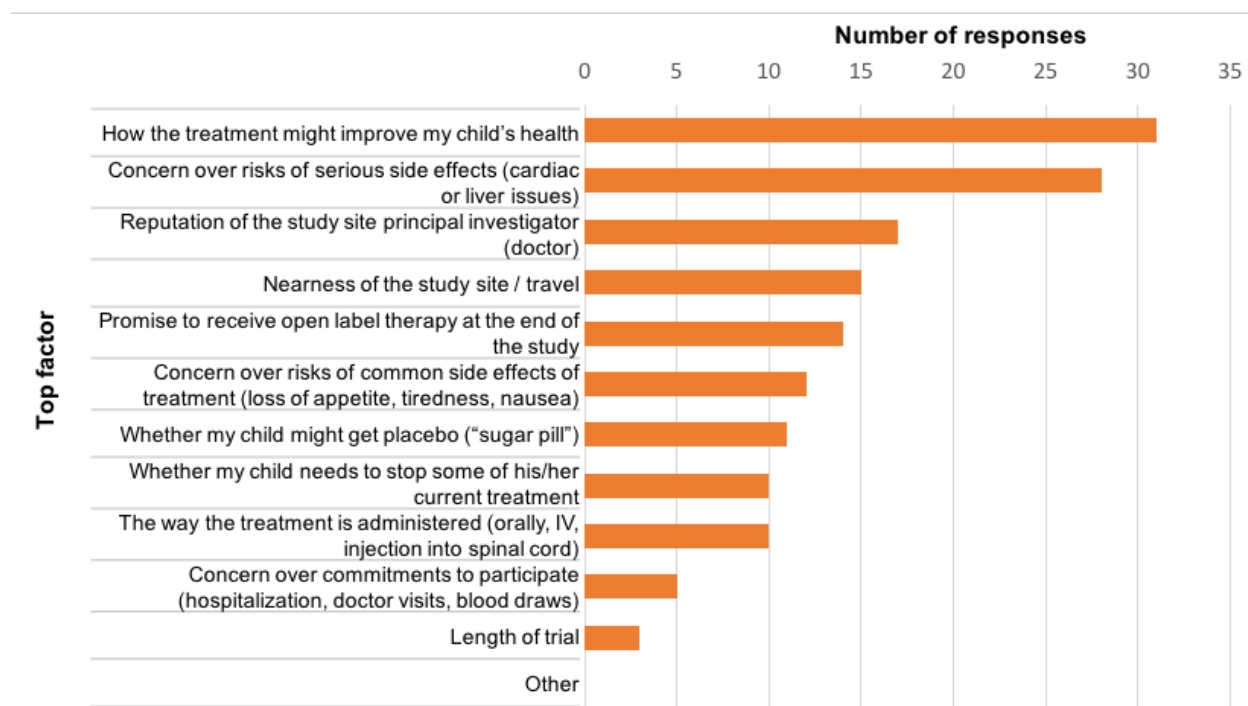
The remainder of the respondents indicated that they would enthusiastically enter a trial if the opportunity presented itself:

- *“We would love to enter one.”*
- *“Will enter such trial without hesitation.”*
- *“I will enter without hesitation.”*
- *“While I'm waiting for cures that are safe with minimal side effects, I am open and willing to try treatments that can improve symptoms.”*

- *“Yes, we would enter one, we are considering it at this time... Any options for treatment are good options for CDKL5 families to consider. We need providers working on options and committed and interested in providing us options.”*

The final question asked respondents what factors would influence their decision to participate in a clinical trial. Though participants were asked to select the top 4 factors, some selected fewer and some more. Among the 156 responses, the top factors chosen were “how the treatment might improve my child’s health,” “concern over risks of serious side effects (cardiac or liver issues),” reputation of the study site principal investigator (doctor), nearness of the study site / travel” (Figure 1).

**FIGURE 1: TOP FACTORS THAT WOULD INFLUENCE YOUR DECISION TO PARTICIPATE IN A CLINICAL TRIAL**



## Incorporating patient input into a benefit-risk assessment framework for CDD

Over the past several years, FDA has developed an enhanced structured approach to benefit-risk assessment in regulatory decision-making for human drugs and biologics. The Benefit-Risk Assessment Framework involves assessing five key decision factors: Analysis of Condition, Current Treatment Options, Benefit, Risk, and Risk Management. When completed for a particular product, the Framework provides a succinct summary of each decision factor and explains FDA's rationale for its regulatory decision.

In the Framework, the Analysis of Condition and Current Treatment Options rows summarize and assess the severity of the condition and therapies available to treat CDD. The assessment provides an important context for drug regulatory decision-making, including valuable information for weighing the specific benefits and risks of a particular medical product under review.

The input provided by patients and patient representatives through the CDD EL-PFDD meeting and survey comments will inform the understanding of the Analysis of Condition and Current Treatment Options for this disease.

The information in the top two rows of the proposed framework for CDD, below, draws from various sources, including what was discussed at the CDD EL-PFDD meeting held on November 1, 2019. This proposed framework contains the kind of information that, if it is anticipated, could be included in a framework completed for a drug under review for CDD. This information is likely to be added to or changed over time based on a further understanding of the condition or changes in the treatment armamentarium.

|                       | EVIDENCE AND UNCERTAINTIES   | CONCLUSIONS AND REASONS  |
|-----------------------|--|--|
| Analysis of Condition | <p>CDKL5 deficiency disorder (CDD) is a rare, x-linked debilitating developmental disorder caused by mutations in the CDKL5 gene leading to deficiencies in the CDKL5 protein which appears to have critical roles in the establishment of neural circuits and synaptic signaling in the brain. Rodent models have demonstrated that deficiencies in the protein negatively impact motor, cognitive, behavioral and physical function.</p> <ul style="list-style-type: none"> <li>• The consequences of CDD are profound and multisystemic:</li> <li>• Refractory epilepsy that is very early onset, presenting within the first few months of life in most, though there are outliers that present later. Individuals with CDD may experience many types of seizures or a mixture of types (tonic, atonic, clonic, myoclonic clusters, and absence seizures) with a range of severity, durations, and frequencies (most often daily) that evolve over the lifetime and with treatment. Seizures might contribute to the neurodevelopmental encephalopathy in CDD.</li> <li>• Global developmental delays that profoundly impair cognition/learning, cortical visual function/eye tracking, gross and motor functions including hand use, ambulation and autonomic functions that lead to hypotonia.</li> <li>• Limited to no ability to communicate verbally, and impaired abilities to use non-verbal communication to alert caregivers to pain or discomfort.</li> <li>• As children grow, behavior issues (laughing/screaming spells) that may be associated with anxiety and sleep disturbances (often several days without sleep).</li> <li>• Constipation, gastrointestinal issues (GI) and dysphagia that may necessitate g-tube placement, and life-threatening respiratory issues.</li> <li>• In adolescence, increasing bone weakness leading to fractures, and scoliosis in some.</li> </ul> <p>Although these symptoms vary from individual to individual—some children may be neurologically impaired but can communicate to some extent and have some mobility for a period, while other have an almost complete absence of motor functions and mobility or eye contact—individuals with CDD are completely dependent on their caregivers for the activities of daily living. In addition, individuals will often lose abilities as they age.</p> <p>CDD also has a profound effect on caregiver and families', emotional, social, psychological and physical health. Caregivers are often exhausted providing care to an individual who is completely dependent upon them to stay alive or for the activities of daily living. Aspects of the disorder can be socially isolating and traumatizing for a family and disruptive of daily life.</p> | <p><b>CDD is a rare inherited debilitating developmental and life-limiting disorder causing profound multisystemic complications that has devastating impacts on the patients and their families' lives, though it varies in severity from one person to the next.</b></p> <p><b>CDD-related seizures are medically refractory, can be very severe, and contribute substantially to neurodevelopmental issues in individuals with CDD.</b></p> <p><b>CDD profoundly impairs neurocognitive development, affecting eye use, hand use and delaying developmental milestones, including ambulation, sometimes indefinitely. CDD thwarts development of communication skills, both verbal and non-verbal. This may be accompanied by anxiety, behavior disturbances, and prolonged periods without sleep. Constipation, GI issues, difficulty swallowing, life-threatening respiratory issues and bone weakness also develop.</b></p> <p><b>All these complications can significantly reduce quality of life.</b></p> <p><b>Individuals with CDD have complex treatment needs for therapies that address both the cause of the disorder, and its consequences.</b></p> |

|  |  |   |
|--|--|---|
| <p style="writing-mode: vertical-rl; transform: rotate(180deg);">Current Treatment Options</p> | <p>Management of the seizures of CDD requires anti-epilepsy drugs (AEDs), though these have limited effect. It is currently treated with special diets and multidisciplinary care and multiple medical or nondrug supportive care therapies of uncertain efficacy, though there may be some symptomatic and palliative benefit. Moreover, individuals with CDD also require assistive communication, mobility equipment and orthotic devices as well as other accommodations in order to participate in the daily activities of living.</p> <p>These treatments only manage the symptoms and clinical consequences of CDD and have many downsides, including the side effects and long-term clinical consequences of lifelong AEDs. Moreover, these treatments are not even effective at treating epilepsy, not to mention, let alone the broader symptoms of global developmental delay. They do not treat the underlying causes of CDD—the deficiency of CDKL5 protein in the brain.</p> <p>Caregivers indicated that what they want most are treatments that improve cognition, the ability to reach developmental milestones, verbal and social communication and gross and motor abilities. After this, they also want better treatments for refractory epilepsy. However, managing GI and respiratory function is also critical to maintain life for some with CDD.</p> <p>Benefit-risk analyses varied with the spectrum of disease severity. Among some caregivers, there was a low risk tolerance while a child with CDD is clinically stable—and concerns about discomfort and side effects when children cannot communicate. Others would weigh the risks of new treatment just as they do with existing treatments, prioritizing quality of life. Those whose children’s lives are most impaired or in greatest jeopardy have a much higher risk tolerance.</p> <p><i>See the Voice of the Patient report for a more detailed narrative.</i></p> | <p><b>There IS an unmet need for effective and tolerable FDA-approved therapies to treat CDD, especially ones that address neurocognitive function/developmental delay, that improve the ability to communicate verbally or non-verbally, and that improve gross and fine motor skills.</b></p> <p><b>Treatments that address the underlying genetic deficiency in CDD may also address the autonomic dysfunction that leads to GI, respiratory and bone complications that can lead to poor quality and even loss of live.</b></p> <p><b>There is also a need for better tolerated AEDs with more durable benefit.</b></p> |
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## Conclusion

The CDD EL-PFDD meeting emphasized the urgent need for increased awareness of CDD, the inadequacy of current treatment for the refractory seizures, and the utter lack of therapeutic options for the global developmental delay associated with the disorder. Clinical experts provided insight into the complex issues faced by clinicians and scientists developing better treatments for this disease. The meeting provided FDA with a unique opportunity to hear in great detail often heart-breaking testimonies directly from caregivers to individuals with CDD who can rarely speak for themselves, and to better appreciate the immense physical and emotional burdens related to living with and caring for someone with CDD.

As Karen Utley said at the meeting’s opening: *“We are in desperate need of disease-modifying treatments and the approval of this type of treatment will require well-chosen measures to capture treatment benefits in clinical trials. This is a daunting reality and we must remedy this quickly. We need the FDA and decisive bodies of government to understand fully that small improvements in our population can make a large impact on the quality of life.”*

After the facilitated discussion, Larry Bauer, who spent 10 years in the Rare Diseases Program within CDER at FDA, summarized some of the meeting’s key themes, which included:

- *CDD is a specific and unique disorder different from all other neurologic disorders.*
- *CDD's seizures are uniquely resistant to treatment—it is not uncommon for some to have daily seizures that last for 15 to 20 minutes.*
- *Another distinctive feature of CDD is the global developmental delay that profoundly affects so many bodily systems—despite the severity of the seizures, health conditions related to this delay are often those that matter most to caregivers.*
- *Among the things that matter to families with CDD are:*
  - *Communication,*
  - *Being able to use our senses fully to express being human,*
  - *Quality of life associated with motor function,*
  - *The ability to use one's hands to make gestures, or to indicate anything, and*
  - *The ability to use one's eyes to track objects or just to communicate,*
  - *The very painful disconnect parents feel when they cannot communicate with their child.*
- *Individuals with CDD are trapped inside bodies that do not allow them to express themselves.*
- *If a treatment was developed leading to the improvement in any of these global symptoms whether for GI disorders, bone problems, communication, cognition, it would be a step forward.*
- *Ultimately, a disease modifying treatment that gets to the underlying cause is need.*

Bauer closed by calling for industry and FDA, to see those with CDD for their potentials, not their symptoms and limitations, to help create a light at the end of the tunnel for them.

Finally, in the formal conclusion of the meeting, Majid Jafar shared how the Loulou Foundation was an eponym for his daughter's nickname, which in Arabic means the big, valuable, rare pearl one gets out of the shells at the bottom of the sea. *"That's exactly what we're trying to unlock,"* he said, by investments to improve clinical translation such as a patient registry, parts of the preclinical toolkit (cellular and animal models, and antibodies), and convening researchers from industry and academia. In addition to the potential treatments in clinical trials, *"we also want the cures that are going to be disease modifying and impact the things we heard today matter so much to the parents and the families and the patients,"* he said before also recapping responses for what the community most wanted from treatment.

*"Although seizures are a big part of our lives and we do want better treatments for those, this is actually so much more than seizures... Improved developmental milestones, improved language ability and social communication and improved motor abilities all ranked higher than improved seizures. Getting to disease modifying treatments that address the global developmental delay are the aspiration of our patient community,"* he said. *"We believe it's doable with the science and the progress, and the number of excellent companies, not only that are in the clinic, but the ones that have active preclinical programs now that we hope will reach the clinic in the coming few years."*

In closing this report, the IFCR and Loulou Foundation are grateful to the caregivers representing CDD symptoms and to the physicians and scientific experts who participated, and to the FDA for their support, participation and for bringing this initiative to life. It is hoped that the content of this VOP will be used to foster the research effort and to guide approvals of much needed therapies in CDD.

As Jafar concluded, *"This was an important milestone, an important chapter, but the work is ahead of us."*

## Appendix 1: CDD PFDD meeting agenda, November 1, 2019

|                       |  |
|-----------------------|--|
| <b>1:30 – 1:40pm</b>  | <b>Welcome and overview</b><br>Karen Utley, President IFCR   |
| <b>1:40 – 1:50pm</b>  | <b>Opening remarks</b><br>Dr Michelle Campbell, Division of Neurology Products, Office of New Drugs, CDER, FDA   |
| <b>1:50 – 2:05pm</b>  | <b>Background on CDKL5 deficiency Disorder:</b><br>Dr Tim Benke, Children’s Hospital Colorado<br>Dr Orrin Devinsky, NYU Langone Comprehensive Epilepsy Center  |
| <b>2:05 – 2:15pm</b>  | <b>Goals and objectives for the meeting, overview of discussion format</b><br>James Valentine, Moderator   |
| <b>2:15- 3:25pm</b>   | <b>Session 1: CDD patient voice: Symptoms and daily impacts</b> <ul style="list-style-type: none"><li>• Panel: Diana Dinescu, Jenny Feinman, Marissa Bishop, Kathy DeSimone, Rick Upp</li><li>• Live Polling</li><li>• Moderated discussion among all meeting participants</li></ul>                             |
| <b>3:25 – 3:35pm</b>  | <b>Break</b>   |
| <b>3:35 – 4:45pm</b>  | <b>Session 2: CDD patient voice: Current and future approaches to treatments</b> <ul style="list-style-type: none"><li>• Panel: Kristin Kozera, Martha Rodgers Boyles, Rita Fredericks, Amanda Jaksha, Ed Fennell</li><li>• Live Polling</li><li>• Moderated discussion among all meeting participants</li></ul> |
| <b>4:45 – 4:55 pm</b> | <b>Closing remarks</b><br>Larry Bauer, Hyman, Phelps & McNamara  |
| <b>4:55 – 5:00 pm</b> | <b>Next steps</b><br>Majid Jafar, Founder Loulou Foundation  |



## Appendix 2: FDA, expert, and meeting panel participants

As of October 31, 120 people had registered for the meeting (this includes live cast in the IFCR pre-event system), 82 of whom attended the meeting in person. Ten more registered on-site. In addition, several members of the FDA were in attendance but had not registered.

The following approximates the patients, caregivers, clinicians, advocates, and industry representatives in attendance:

- **Patients:** 10
- **Caregivers/family members:** 45
- **Advocacy representatives:** At least 10
- **Clinicians/CDD specialists:** 3
- **Industry representatives:** 22

FDA representatives who attended the meeting included:

| Name                  | Position   | Division  |
|-----------------------|--|---|
| Anne Rowzee           | Associate Director for Policy, Office of Tissues and Advanced Therapies  | Center for Biologics Evaluation and Research (CBER)               |
| Billy Dunn            | Director of the Office of Neuroscience                                   | Center for Drug Evaluation and Research (CDER)                    |
| Cynthia Welsh         | Medical Officer  | CDER  |
| Eleanor Dixon-Terry   | Regulatory Health Program Manager  | Office of Orphan Products Development                             |
| Julienne Vaillancourt | Rare Disease Liaison   | CBER  |
| Karen Jackler         | Patient Engagement Lead  | CBER  |
| Lei Xu                | Chief of General Medicine Branch   | Office of Tissue and Advanced Therapies, CBER                     |
| Lucas Kempf           | Medical Officer  | Rare Diseases Program, CDER                                       |
| Michelle Campbell     | Senior Clinical Analyst for Stakeholder Engagement and Clinical Outcomes | Division of Neurology Products, CDER                              |
| Mike Singer           | Medical Officer  | Division of Clinical Evaluation and Pharmacology/Toxicology, CBER |
| Susan McCune          | Director of the Office of Pediatric Therapeutics                         |   |

## Appendix 3: CDD EL-PFDD Meeting Polling Questions and Results

### Demographic questions

#### 1. Where do you currently reside? (58 respondents/responses)

| Region                   | Count (Responses) | Percentage |
|--------------------------|-------------------|------------|
| US Northeast             | 20                | 34%        |
| US Midwest               | 13                | 22%        |
| US South                 | 9                 | 16%        |
| US West                  | 5                 | 9%         |
| US Pacific               | 1                 | 2%         |
| Mexico or Canada         | 0                 | 0          |
| Outside of North America | 10                | 17%        |

#### 2. In what type of residential area do you live? (50 respondents/responses)

| Residential area | Count (Responses) | Percentage |
|------------------|-------------------|------------|
| A city           | 19                | 38%        |
| A rural area     | 5                 | 10%        |
| A suburban area  | 26                | 52%        |

#### 3. What is your child's race or ethnicity? (55 respondents/responses)

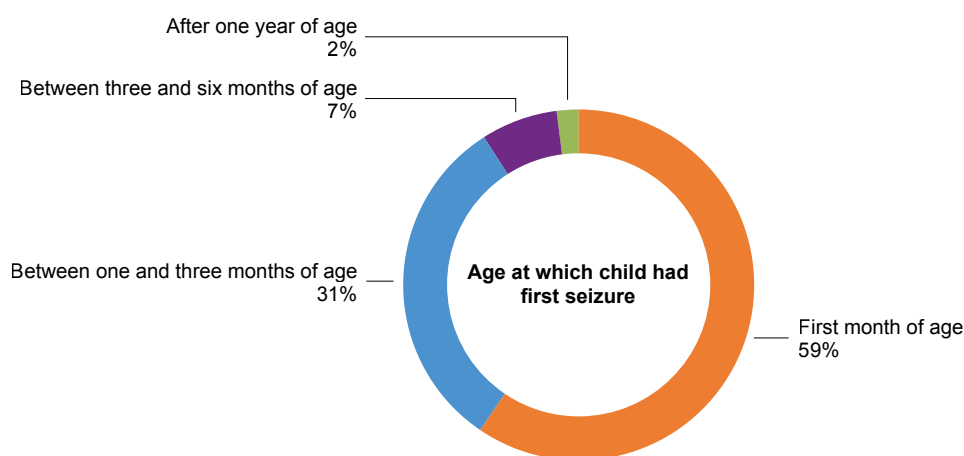
| Ethnicity                                 | Count (Responses) | Percentage |
|---|-------------------|------------|
| American Indian or Alaskan Native         | 0                 | 0%         |
| Asian                                     | 3                 | 5%         |
| Black or African American                 | 1                 | 2%         |
| Native Hawaiian or other Pacific Islander | 0                 | 0%         |
| Multiracial                               | 5                 | 9%         |
| White                                     | 44                | 80         |
| Other                                     | 2                 | 4%         |

#### 4. What is your child's sex? (52 respondents/responses)

| Sex    | Count (Responses) | Percentage |
|--------|-------------------|------------|
| Male   | 9                 | 17%        |
| Female | 43                | 83%        |

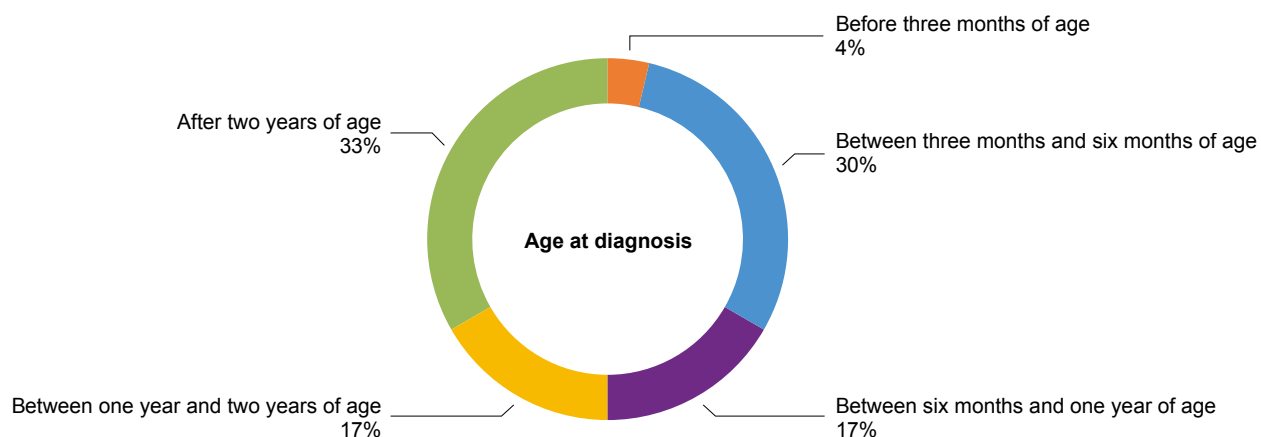
### 5. At which age did your child have his/her first seizure? (54 respondents/responses)

| Age                                  | Count (Responses) | Percentage |
|--------------------------------------|-------------------|------------|
| First month of age                   | 32                | 59%        |
| Between one and three months of age  | 17                | 31%        |
| Between three and six months of age  | 4                 | 7%         |
| Between six months and a year of age | 0                 | 0%         |
| After one year of age                | 1                 | 2%         |



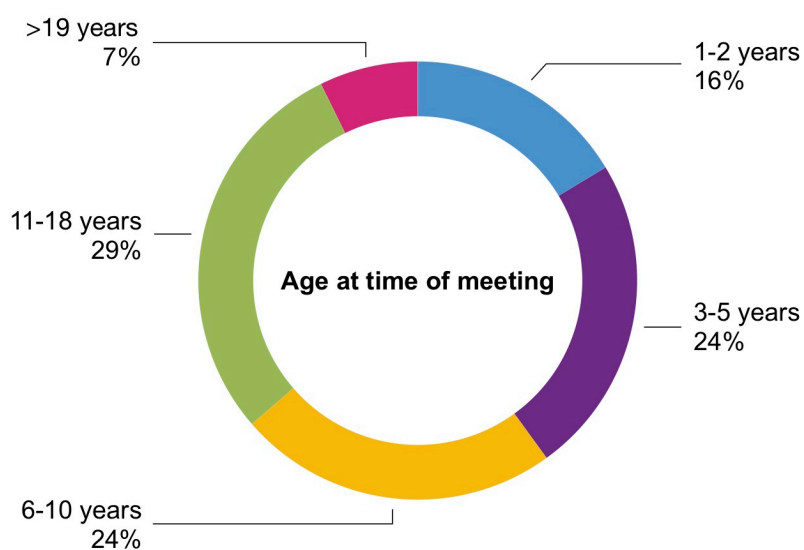
### 6. At which age was your child diagnosed with CDD? (54 respondents/responses)

| Age  | Count (Responses) | Percentage |
|--|-------------------|------------|
| Before three months of age                 | 2                 | 4%         |
| Between three months and six months of age | 16                | 30%        |
| Between six months and one year of age     | 9                 | 17%        |
| Between one year and two years of age      | 9                 | 17%        |
| After two years of age                     | 18                | 33%        |



## 7. How old is your child? (55 respondents/responses)

| Age of child at time of poll | Count (Responses) | Percentage |
|------------------------------|-------------------|------------|
| <1 year                      | 0                 | 0%         |
| 1-2 years                    | 9                 | 16%        |
| 3-5 years                    | 13                | 24%        |
| 6-10 years                   | 13                | 24%        |
| 11-18 years                  | 16                | 29%        |
| >19 years                    | 4                 | 7%         |

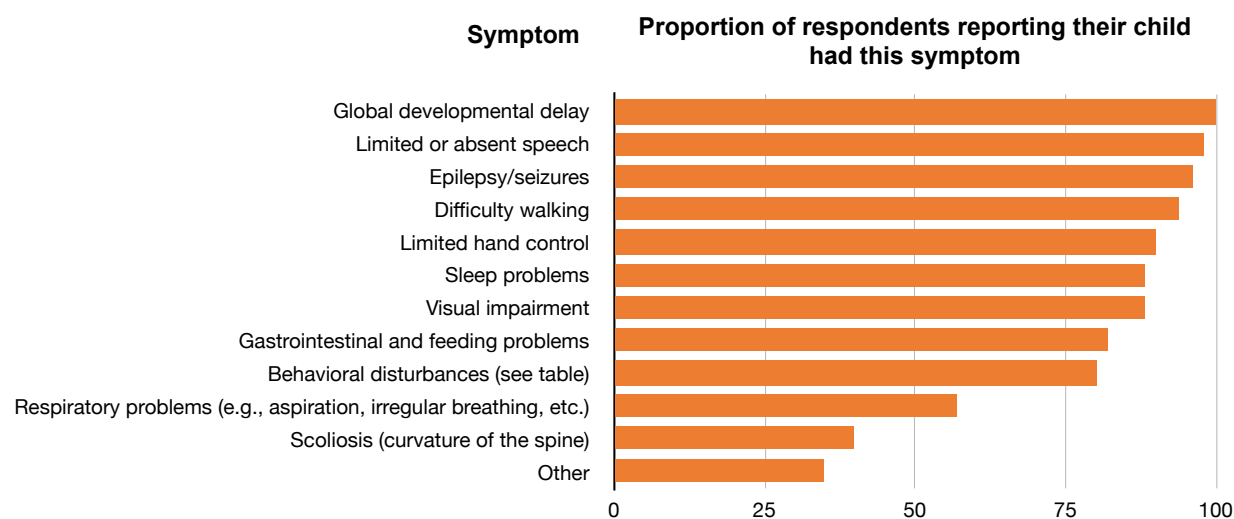


## Topic 1 LIVING WITH CDD: SYMPTOMS AND DAILY IMPACT

### 8. Which of the following CDD-related symptoms and health effects does your child have currently?

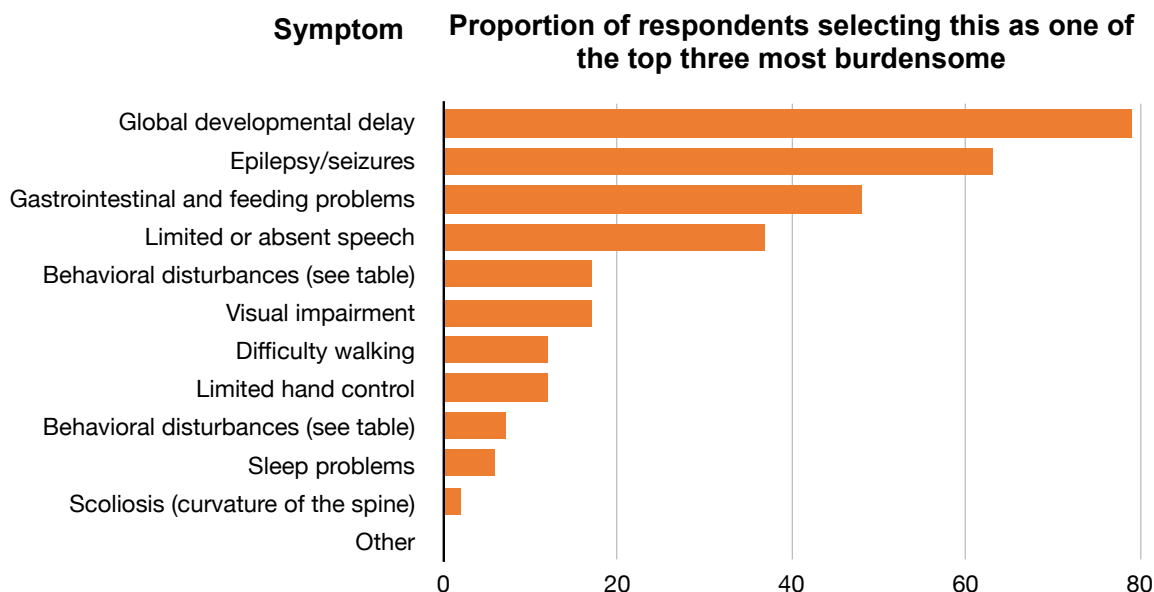
Select ALL that apply (49 respondents/464 responses)

| Symptoms   | Count (responses) | Proportion of respondents making this selection |
|--|-------------------|---|
| Epilepsy/seizures  | 47                | 96%   |
| Difficulty walking   | 46                | 94%   |
| Global developmental delay   | 49                | 100%  |
| Scoliosis (curvature of the spine)   | 20                | 40%   |
| Limited hand control   | 44                | 90%   |
| Visual impairment  | 43                | 88%   |
| Limited or absent speech   | 48                | 98%   |
| Gastrointestinal and feeding problems  | 40                | 82%   |
| Respiratory problems (e.g., aspiration, irregular breathing, etc.)   | 28                | 57%   |
| Behavioral disturbances (e.g. hypersensitivity, agitation, irritability, stereotypies, bruxism, self-injury) | 39                | 80%   |
| Sleep problems   | 43                | 88%   |
| Other  | 17                | 35%   |



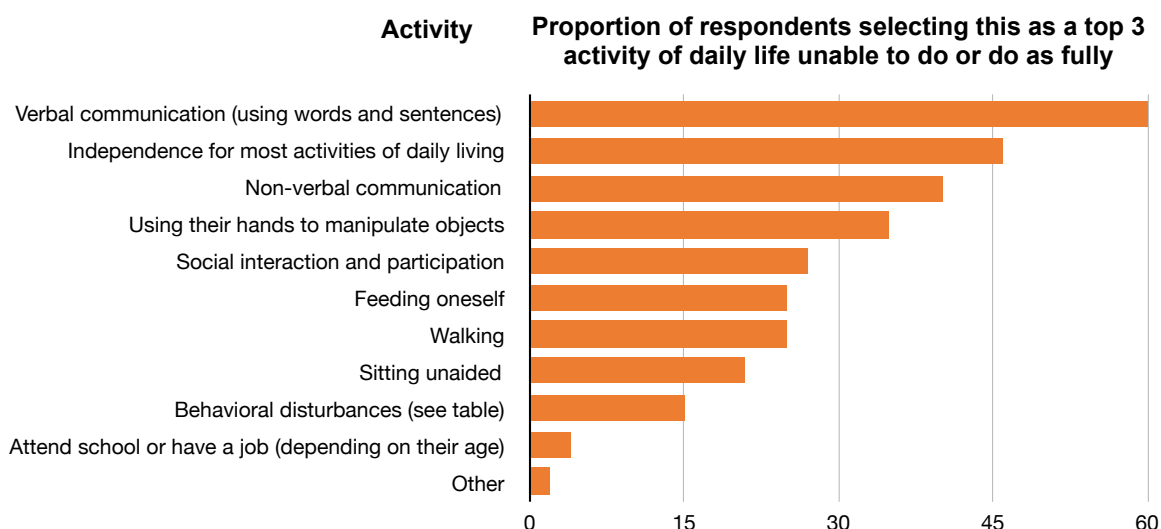
**9. Select the **TOP 3** CDD-related symptoms and health effects that are most burdensome for your child  
(52 respondents/156 responses)**

| Symptoms   | Count<br>(responses) | Proportion of respondents<br>making this selection |
|--|----------------------|--|
| Epilepsy/seizures  | 33                   | 63%  |
| Difficulty walking   | 6                    | 12%  |
| Global developmental delay   | 41                   | 79%  |
| Scoliosis (curvature of the spine)   | 1                    | 2%   |
| Limited hand control   | 6                    | 12%  |
| Visual impairment  | 9                    | 17%  |
| Limited or absent speech   | 19                   | 37%  |
| Gastrointestinal and feeding problems  | 25                   | 48%  |
| Respiratory problems (e.g., aspiration, irregular breathing, etc.)   | 4                    | 7%   |
| Behavioral disturbances (e.g. hypersensitivity, agitation, irritability, stereotypies, bruxism, self-injury) | 9                    | 17%  |
| Sleep problems   | 3                    | 6%   |
| Other  | 0                    | 0%   |



**10. What specific activities of daily life are most important to you that your child is NOT able to do or do fully due to CDD? **Select TOP 3** (48 respondents/144 responses)**

| Activities of daily life  | Count (responses) | Proportion of respondents making this selection |
|---|-------------------|---|
| Walking   | 12                | 25%   |
| Sitting unaided   | 10                | 21%   |
| Using their hands to manipulate objects   | 17                | 35%   |
| Feeding oneself   | 12                | 25%   |
| Independence for most activities of daily living  | 22                | 46%   |
| Non-verbal communication (e.g., using gestures and facial expressions to communicate with others) | 19                | 40%   |
| Verbal communication (using words and sentences)  | 29                | 60%   |
| Have regular sleep patterns   | 7                 | 15%   |
| Social interaction and participation  | 13                | 27%   |
| Attend school or have a job (depending on their age)  | 2                 | 4%  |
| Other   | 1                 | 2%  |





## Topic 2 - PERSPECTIVE ON CURRENT AND FUTURE APPROACHES TO TREATMENT

**11. What medications or treatments is your child currently using? Select ALL that apply (46 respondents/165 responses)**

| Medication   | Count (responses) | Proportion of respondents making this selection |
|--|-------------------|---|
| Anti-epileptic drugs (including Epidiolex)                           | 45                | 98%   |
| Steroid treatment  | 2                 | 4%  |
| Experimental medications as part of a clinical trial/expanded access | 9                 | 20%   |
| Formulations of medical cannabis including CBD                       | 12                | 26%   |
| Vagus nerve stimulator (VNS)   | 11                | 24%   |
| Sleep medication   | 21                | 46%   |
| Neurosurgery   | 0                 | 0%  |
| Ketogenic diet   | 17                | 37%   |
| Supplements  | 33                | 72%   |
| Other  | 15                | 33%   |

**12. What are you currently doing to help manage the symptoms of CDD? Select ALL that apply (49 respondents/365 responses)**

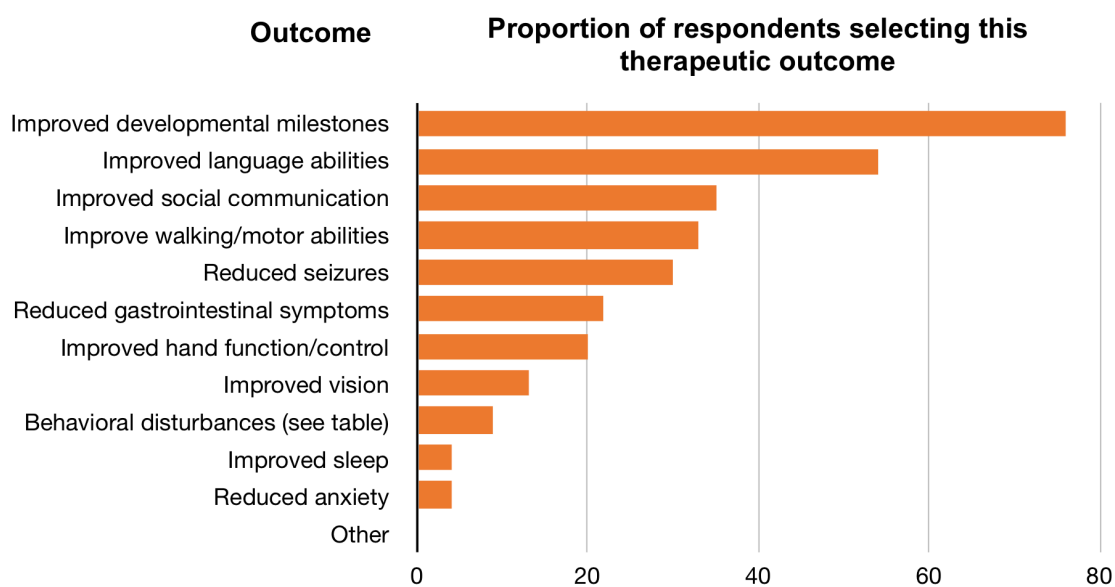
| Therapeutic Approach   | Count (responses) | Proportion of respondents making this selection |
|--|-------------------|---|
| Physical therapy   | 44                | 90%   |
| Occupational therapy   | 41                | 84%   |
| Speech therapy   | 39                | 80%   |
| Hippotherapy (horse therapy)   | 7                 | 14%   |
| Hydrotherapy (water therapy)   | 21                | 43%   |
| Orthotics support (back brace, foot braces)                            | 32                | 65%   |
| Modifications/accommodations at home                                   | 33                | 67%   |
| Eye gaze speech production device                                      | 16                | 33%   |
| Mobility equipment (adaptive strollers, wheelchairs)                   | 36                | 73%   |
| Nutritional support (nasogastric tube, g-tube)                         | 19                | 39%   |
| Approved pharmacological therapies (e.g. approved antiepileptic drugs) | 46                | 94%   |
| Investigational products (clinical trials)                             | 11                | 22%   |
| Other  | 20                | 41%   |

**13. In general, how much have the medications and other treatments helped improve your child's quality of life? (43 respondents/43 responses)**

| Impact of Treatment    | Count (responses) | Proportion of respondents making this selection |
|------------------------|-------------------|---|
| No change              | 2                 | 5%  |
| Slightly improved      | 28                | 65%   |
| Moderately improved    | 4                 | 9%  |
| Substantially improved | 7                 | 16%   |
| Not sure               | 2                 | 5%  |

**14. Which ability or symptom would you rank as most important for a possible drug treatment today?**  
**Select up TOP 3 (46 respondents/138 responses)**

| Therapeutic Approach              | Count<br>(responses) | Proportion of respondents making this<br>selection |
|-----------------------------------|----------------------|--|
| Reduced seizures                  | 14                   | 30%  |
| Improved developmental milestones | 35                   | 76%  |
| Improved hand function/control    | 9                    | 20%  |
| Improve walking/motor abilities   | 15                   | 33%  |
| Improved vision                   | 6                    | 13%  |
| Improved language abilities       | 25                   | 54%  |
| Improved social communication     | 16                   | 35%  |
| Reduced gastrointestinal symptoms | 10                   | 22%  |
| Improved sleep                    | 2                    | 4%   |
| Reduced discomfort                | 4                    | 9%   |
| Reduced anxiety                   | 2                    | 4%   |
| Other                             | 0                    | 0%   |



## Appendix 4 - Related materials

Additional materials available at [www.cdkl5.com/PFDD](http://www.cdkl5.com/PFDD) including:

- PFDD meeting video recording
- Meeting program booklet including agenda and speaker bios
- CDKL5 Deficiency PFDD Post-Meeting Survey and Responses