

PDCD



FDA Listening Session

The Voice of the Pyruvate Dehydrogenase Complex Deficiency (PDCD) Patient Community



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Patient-led Listening Session
with the U.S. Food & Drug Administration

September 8, 2023

Objective of session

The PDCD patient community seeks to establish deeper relationships with the FDA reviewers to foster dialogue for future regulatory deliberations. We believe the sharing of patient and caregiver experiences and preferences will provide FDA staff with a better understanding of PDCD and demonstrate the community's urgent unmet medical need.

About Pyruvate Dehydrogenase Complex Deficiency

Pyruvate dehydrogenase complex deficiency (also known as PDC deficiency, or more commonly PDCD) is a rare mitochondrial disorder that causes impaired carbohydrate metabolism. This impairment results in neurological problems and the buildup of a chemical called lactic acid in the blood.

PDCD is caused by mutations in the genes that make up or affect the activity of the PDC. The PDC is located in the mitochondria, the cell's "powerhouse" that makes almost all the energy we need to survive. The PDC is vital in converting the carbohydrates we eat into adenosine triphosphate (ATP), which act as the "currency" to our cells. Thus, when the PDC is defective, our cells suffer from a lack of ATP to spend on energy, and the signs and symptoms of PDCD reflect such energy failure. An estimated 85% of cases of PDCD are caused by a mutation in the PDHA1 gene. Other genes that have been linked to PDCD include DLAT, DLD, PDHB, PDHX, and PDP1. Although mutations that cause PDCD can be inherited, the majority appear by chance.

The age of onset and the severity of the symptoms of PDCD vary widely among affected individuals. The disorder can present before birth, as brain abnormalities detected by routine ultrasound; during infancy or early childhood, as developmental delay and chronic neurologic symptoms, including seizures; or rarely, in late childhood as a movement disorder such as ataxia. In general, individuals with PDCD symptom onset before birth or in infancy die during childhood, sometimes from lactic acidosis. Those that present later may survive into adulthood.

The frequency of the disease is estimated to be 1 in 50,000.

There is no U.S. Food and Drug Administration-approved treatment or cure for PDCD. As such, clinicians traditionally recommend symptom management and general supportive care such as a ketogenic (keto) diet for developmental delay, seizures, and incoordination and physical and occupational therapy to help with muscle function.

Summary

Seven caregivers - including one caregiver who was also an affected adult - to PDCD patients participated in the Listening Session via videoconference, along with clinician Dr. Rebecca Ganetzky of Children's Hospital of Philadelphia. Patients represented ranged in age from 1 to 32.

Outlined below are summaries for each speaker, along with some key themes from the session, including direct quotes about the burden of living with PDCD, current treatments, tolerance for risk in trying new treatments, and the most valued outcomes for potential treatments.

Summary: Father to a 25-year-old son affected by PDCD

The first sign something was wrong was low activity early on in life. He would also sleep through the night in the exact same place he was placed in the crib. The family's pediatrician assured them children develop at different rates, but after a few months without progress, their child was diagnosed with PDCD. The family was told he would not live past his teens.

At age 17, the patient developed psychosis and mental health issues. The family believes this is related to PDCD, with most patients simply not living long enough to develop such symptoms.

Today, the patient is relatively stable health-wise thanks to the ketogenic diet but has a mild physical disability and is cognitively impaired, which limits his ability to work.

They hope this session will enhance potential treatments.

Summary: Father to a 19-year-old daughter affected by PDCD

The father shared anecdotes from his daughter's childhood: age 2, severe weakness meant the family had to feed her via syringe every 15 minutes; age 4, she was in and out of hospitals due to recurrent fevers, loss of mental status, and acidosis, and they were told to prepare for her to die; age 6, required intensive support just to sit up, which would leave her winded; age 8, still non-verbal and able to tolerate only a few hours of school a day; age 10, faced severe hip dysplasia and unable to take even 20 steps with support; age 14, worsened developmental disability with additional diagnoses of autism and anxiety; age 19, sturdier, but unable to speak or care for herself.

Early access to treatments is critical. He encouraged the FDA to recognize that a successful treatment, even with only incremental improvement, could have had a profound impact later in her life. Given the disease's devastating impact, the family is willing to accept treatment risk with even small benefits.

He noted that despite medical advances since her diagnosis nearly 20 years ago, not much has changed in the way her disease and symptoms are managed that would give her a better quality of life.

Summary: 32-year-old mother affected by PDCD and caregiver to a 4-year-old son affected by PDCD

Other than gait issues as a child, the speaker considered herself healthy. She had gastric bypass surgery approximately 10 years ago so she could one day have children, which seems to have kick-started issues. After the surgery, her body began eating her muscles and organs to survive. She lost the ability to walk or stand and had severe nerve pain and stroke-like episodes.

After four years with no answers, she found out she was pregnant. The child was born with low blood sugar, jaundice, and an under-formed lung, but otherwise healthy. Three years later, at the mother's age of 31, and the son age 3, both received an official diagnosis of PDCD.

The mother was diagnosed with dysautonomia and postural orthostatic tachycardia syndrome (POTS) which causes her autonomic nervous system to malfunction, leading to temporary vision loss and passing out. She also reported sharp nerve and muscle pain which worsens at night, perforated

intestine which required surgery, gastroparesis, esophageal dysmotility, hypo-hidrosis, diminished temperature sensation, along with many vitamin deficiencies. All issues are worsened by stress. Both patients are on the ketogenic diet.

She urged FDA staff to ensure access to clinical trials to all age groups, noting that her son was eligible for a PDCD trial and she was not. She also encouraged better labeling of sugar-free products, noting that her son only can have 10g of carbohydrates per day but, due to a rounding loophole, many items can claim to be sugar-free when they are not which creates severe health risks for PDCD patients. She also advocated for more carbohydrate-free over-the-counter medicines, vitamins, and prescriptions.

Summary: Mother to a 15-month-old daughter affected by PDCD

Her daughter was one of the first children to be diagnosed with PDCD in utero. At her 12-week ultrasound, doctors observed fetal brain abnormalities, which led to a PDCD diagnosis 19 weeks into the pregnancy.

PDCD impacts her daughter's brain and muscle development, hearing, vision, speech, and motor skills. Her daughter cannot sit up by herself, crawl, walk, talk, and struggles with energy levels.

She credits early intervention and the ketogenic diet for improving her daughter's outlook but worries about the lack of treatments that could improve her obstacles and quality of life.

The patient currently receives physical, occupational, vision, and feeding therapies, in addition to therapeutic "mito cocktail" medications such as acetylcysteine, riboflavin, and thiamine in hopes of defending against the degenerative nature of the disease.

She worries most about the development of seizures and consumption of carbohydrates or sugars that would risk lethal metabolic acidosis.

Given the grim prognosis of PDCD patients, the family is hopeful for a treatment quickly. They feel gene therapy and early diagnosis are promising, with hopes that a small molecule therapy - like the clinical trial their daughter is currently enrolled in - could help bridge the gap while things progress.

Summary: Mother to a 19-year-old daughter affected by PDCD

She reports her daughter, who was diagnosed at 18 months of age and is now age 19, is totally dependent upon others for her survival, including to feed, dress, move, medicate, and bathe her.

Pain is a major aspect of the disease. Her daughter has constant muscle pain, but her lack of speech keeps her from communicating what's hurting. Such pain also keeps her from sleeping more than a few hours a night, allowing for almost no regenerative sleep.

The disease leaks into almost all aspects of the family's day. A good day is when pain medication controls muscle pain and the patient can participate in school activities. Bad days - which she reports are more frequent now - mean 2-3 hours of uncontrollable, severe pain. The pain is frequently joined by "low energy" days, where the patient loses nearly all motor function.

The degenerative nature of the disease has also meant the loss of function that existed at younger ages, such as walking and speaking. The family lives in "crisis mode" daily, worried about greater mental and physical regression or even death.

The patient uses a ketogenic diet to provide cellular energy, but it has contributed to severe osteoporosis. She has had 52 orthopedic surgeries and several fractured bones. She has also been hospitalized hundreds of times for respiratory illness, because her body cannot fend off minor viruses.

She takes sodium bicarbonate to avoid acidosis, a cocktail of supplements for bone health, fat processing, along with narcotics and muscle relaxants for pain, but it does nothing to stop progression.

The family is looking for something that would improve energy output, increase function, and inhibit cellular death, thus creating a better quality and quantity of life such as stronger muscles for tone, speaking, eating, and breathing.

Given that a slow and painful death seems the only other option, the family is open to assuming risk for a new treatment. They would like to see the rapid approval of repurposed FDA-approved treatments as well as streamlined approval of studies for novel, promising therapies and therapeutics.

Summary: Mother to a 3-year-old daughter with PDCD

Despite a few small issues at birth such as failing a hearing test, the family left the hospital with a seemingly healthy baby girl. Over the next few months, hearing loss was confirmed but now with developmental issues and atypical muscle tone.

At age four months, an MRI showed the child's brain was severely underdeveloped. After additional issues arose, whole exome sequencing led to a PDCD diagnosis at 10 months old.

The family immediately began a ketogenic diet and feels that the delayed diagnosis - the 10 months with a non-ketogenic diet - made the disease progress, which could have been avoided if PDCD was included on newborn screening.

Today at age three, the hardest symptom to manage is seizures. She was diagnosed with infantile spasms, which are managed with medications - but focal seizures are a large part of her life. She has had a positive reaction to medical CBD, but they have not found any medications that work without major side effects. On good days, the patient may only have a few seizures. On bad days, it could be up to 20.

Despite this, the child's personality and interactions with her surroundings have blossomed. She cannot walk or talk, but she finds ways to communicate. The family is trialing an adaptive communication device and reports positive results.

They continue to work on mobility due to worries around losing milestones and skills. She attends physical, occupational, feeding/speech, and aquatic therapies. Before her diagnosis, she attended daycare but was pulled out due to inability to fight common viruses without a hospital visit.

The family believes the best chance at extending life for patients is via gene therapy and small molecule therapy.

Summary: Mother to a 3-year-old daughter affected by PDCD

For nearly two years, the family desperately tried to find an explanation for their daughter's developmental delays, seizures, aspiration, choking episodes, and kidney stones. At 21 months, she was diagnosed with PDCD.

At this time, the child was referred to a dietician and placed on a ketogenic diet, which brought immediate results. She went from an unsteady toddler, who could only scoot a few inches before tiring, to crawling and standing within a week. The family feels this extended diagnostic journey - and lengthened period without any treatment and special diet - worsened their daughter's PDCD symptoms and believe PDCD should be added to newborn screening.

At age two, they started a clinical trial and report positive results, including new movement - what they call "new joy and lightness," as well as relief from pain, exhaustion, and gastrointestinal issues. They also noticed additional mental acuity, including new words, interest in complex toys, and consciousness of her surroundings.

With that said, the family still needs more from future treatments. Even with the ketogenic diet and trial, their daughter struggles with energy levels, gastrointestinal issues, and choking events where she abruptly stops breathing.

She urged the FDA and drug developers to consider the needs of PDCD patients when considering flavor additives to treatments, mentioning aspartame flavoring in a trial as a cause of major issues for her child.

They are interested in pursuing small molecule therapies, gene therapies, and advancements in managing a keto diet and are willing to take a risk for improved quality of life.

Follow-up Questions

James Valentine of Hyman, Phelps & McNamara helped moderate the session and asked several follow-up questions.

Putting aside a complete cure for PDCD, what would be valuable in future treatments for PDCD?

Caregiver: Something to improve hypotonia and weakness. Her world is very small because of muscle fatigue. She gets worn out from just a few minutes of physical therapy. She has very weak core

strength.

Patient (and caregiver): Something that would allow myself and my son to consume more carbohydrates and not limit him to 10 carbohydrates per day. Sleep improvement would greatly help with other areas of life.

Caregiver: More flexibility in what we could feed our son. Something labeled keto on a store shelf can't be fed to him. Something that could stop the progression of the disease, prevent organ decline, and neurodegeneration.

Caregiver: What gets lost is that carbohydrates are life-threatening and scary. Anything that would provide energy to the cells would be life-preserving.

Caregiver: My daughter is very severe. We work hard just to maintain her status quo. Slowing the progression of the disease is my biggest concern. We'd want something to help hit more physical milestones and to continue doing speech therapy. Keeping her muscles strong is very important and will play a huge factor as the disease progresses.

Caregiver: The number one thing is slowing or stopping the progression of symptoms. On the trial, we have seen significant improvements since our daughter has been able to stand and bear weight. Her gastrointestinal symptoms, her aspiration, and her sleep have all improved. Before she was able to crawl, the reflux and aspiration were very bad.

Caregiver: Stability and incremental gains in function would be great. A lot of unknowns about him decompensating from a virus or changing things.

Question: How do you determine improvements?

Caregiver: Moving her body more, less constipation, eating more by mouth. Step-by-step benefits.

Caregiver: Looking for stability and increment improvements. We are concerned about stability. Is he one good virus away from decompensation? When is the other shoe going to drop?

A clinician's view

Dr. Rebecca Ganetzky of Children's Hospital of Philadelphia (CHOP) joined the session to talk about her experience treating approximately 50 patients with PDCD. These patients span a wide range of ages - the oldest is currently 47 - and severity. She estimates she diagnoses 10 new patients a year, who are often local to her hospital. She believes PDCD is underdiagnosed and much more common than estimated. She encouraged more research into gene therapy, enzyme replacement therapy, and drug screening for PDCD treatments.

FDA follow-up questions

FDA's Division of Clinical Outcome Assessment asked several follow-up questions.

Question: The use of augmentative and alternative communication (AAC) devices was mentioned earlier. Has anyone used them?

Caregiver: Yes, we have an AAC device. Honestly, it is progressing with speech. We spent a long time setting up the device while she was progressing. We have high hopes for using it with more complex needs.

Caregiver: Our child used an AAC device starting at age 5 or 6. Its accuracy used to be a lot better. With the progression of the disease and her ataxia being so much worse it became difficult to push buttons as she ended up dragging her hand. It became frustrating for her. She uses vocalizations and gestures instead.

Question: Can you give some examples of how symptoms can fluctuate?

Caregiver: He has bilateral brain lesions, so on bad days the lesions have a greater effect. On a very mild day, he can walk and talk. If it's a bad day, he'll just fall over. You never know what he'll fall into. His legs will be wobbly. Ataxia kicks in. On a good day, he goes to preschool and has a good vocabulary. On a bad day, you can tell. It's night and day.

Caregiver: The thing we look out for is lethargy. Weak and low-toned. That's an indication when we need labs drawn or new meds. Even when they can't communicate, it's present.

Caregiver: My son can communicate and can talk, but the psychosis takes over and disconnects him from reality. We use drugs like Ativan, sometimes it works, but sometimes we have to just sit with him for hours. Our belief is that's a symptom of mitochondrial disease.

PDCD survey

A survey, which was distributed by participating patient advocacy groups a few months prior to the session, was taken by 57 patients affected by PDCD and their caregivers. Results from this survey were presented during the session and are cited several times below.

Survey Results & Direct Quotes from Patients and Caregivers

During the session, FDA staff heard participants describe PDCD as a disease that progresses with remarkable speed to severely affect the ability to eat, walk, talk, breathe, and sleep - and, ultimately, to continue living. These concerns largely mirror survey results.

Muscle weakness:

As with most mitochondrial diseases, severe muscle weakness is one of the most common symptoms reported by PDCD patients. More than 84% of survey respondents cited muscle

weakness as one of the three most impactful symptoms, making it the most common response. Such weakness has drastic outcomes for many patients such as a struggle to walk, stand, talk, or eat. Below are some quotes from listening session participants regarding these struggles.

- *She used to **walk** with assistance. Eventually she lost the ability to support her weight at age 8. Now, she must be lifted and carried and propped when not using her wheelchair.*
- *Because of PDCD, (she) will never **walk**, or **talk**, or care for herself.*
- *My body started to eat my own muscles to survive, and my organs were shutting down. Over a matter of days, I lost the ability to **stand** or **walk**.*
- *(She) is 15 months old and cannot **feed** herself, sit up by herself, crawl, **walk**, **talk** - all things typical children her age can do.*
- *Will she ever be able to **walk**? Or **talk**? Will she be able to attend school? And if so, develop socially age-appropriate friendships?*
- *They say that only when we have walked in the shoes of another, can we begin to fully understand their journey of fear, sorrow, doubt, fatigue, and even laughter and dreams. We have not walked in (her) shoes because (she) has never been able to **walk** on her own. But, (we) have, however, walked beside her, literally step by step for 19 years.*
- *In the first year of her life, we were not sure if she would be able to ever smile intentionally or interact with loved ones. Although she cannot **walk** or **talk**, she certainly can communicate with those who know her best.*
- *She suffers from terrible daily pain, but the lack of **speech** inhibits her ability to tell us what is hurting.*
- *We haven't **heard a discernable word** from her since she was about 9 years old. Now, she just has vocalizations. She cannot advocate for her wants and needs and thus we have watched her spirit dim without the ability to communicate with those around her.*
- *She was 2 and **could barely swallow** due to severe muscle weakness, requiring around-the-clock small high-caloric feeds and daily PT on her tiny facial muscles. This literally meant **feeding** her by mouth via a 10 cc syringe every 15 minutes in order to avoid dependence on a g-tube, in addition to daily passive motion exercises to support the development of her weak tiny facial muscles.*

Energy and fatigue:

Nearly 56% of survey respondents reported chronic fatigue - including tiredness, excessive sleeping, brain fog, or mental fatigue - as one of the three most impactful symptoms of PDCD. During the listening session, participants commented similarly.

- *Just sitting upright for a while left her **fatigued** as if she had just run a mile.*
- *(She) struggles to maintain enough energy to get through the day. She can walk with her walker for short distances, but any rough terrain or longer outings cause her to tire quickly and needs to be carried or pushed in a stroller.*
- *We still see (her) struggle with her **energy** levels. Some may say she is a great sleeper, but as parents we know the metabolic reason behind her multiple naps throughout the day. “Low **energy**” days can trigger a complete loss of muscle function, no ability to hold her head or body up, or even to make her eyes focus.*
- *She does not have friends because she doesn’t have the **stamina** nor the ability to participate in social activities.*
- *I have poor **endurance** and need frequent rest periods.*
- *“Low **energy**” days can trigger a complete loss of muscle function, no ability to hold her head or body up, or even to make her eyes focus.*

Developmental disabilities and delays:

In the survey, 52% of survey respondents described PDCD as causing a high level of impairment, meaning profound developmental or cognitive delay and significant support to do age-appropriate activities and tasks.

- *(He) has a mild physical disability, but he is **cognitively impaired**. Essentially, he is a cognitive 9-year-old in a 25-year-old body. This limits his ability to work, and he attends day programs.*
- *At age 14, (her) **developmental disability** worsened so much that she got additional diagnoses of autism and anxiety. Another diagnosis compounding the underlying metabolic defect, inability to walk, communication challenges, developmental delay, fatigue, muscle weakness and fragility that is every day while living with PDCD.*

- *The beginning seems like a logical place to start, but unfortunately, we don't have time to cover the months of hopeless searching, desperately trying to find an explanation for my daughter's **development delays**, seizures, aspiration and choking episodes, kidney stones, and a host of other symptoms.*
- *She is now 15 months old and has brought us more joy than we could have ever imagined. However, she has been impacted with both **brain** and muscle **development**, hearing loss, vision impairment, **speech and motor delay**, all that comes with a PDCD diagnosis.*

On top of such delays, caregivers on the session frequently reported related struggles such as autism, anxiety, and mental health issues.

- *At age 14, when the fatigue of caregiving became so profound that my wife and I felt we could barely go on, and (her) **developmental disability** worsened so much that she got additional diagnoses of **autism** and **anxiety**.*
- *At age 17, (he) developed psychosis. **Mental health** issues are not well understood as they relate to Mitochondrial Disease and the ability to control these symptoms in conjunction with the keto diet and other treatments has posed a challenge that we have yet to conquer. Our belief is that the issue is that many of the PDCD children don't live long enough to develop these symptoms and/or those that live past their teens may be mildly affected and either misdiagnosed or not diagnosed.*

More severe symptoms:

While weakness, fatigue, and developmental delays were some of the most common issues, they were not always the most concerning. Both session testimony and the survey showed, despite lower incidence, greater concern for more life-threatening symptoms, including acidosis and seizures. Nearly all patients or caregivers who had experienced such issues rated them as causing "significant worry."

Acidosis:

- *The risk of **acidosis** is constantly prevalent, and we must closely monitor her ketones several times a day.*
- *Any improvement over time to her chronic metabolic **acidosis** and metabolic stress may have diverted metabolic strokes so there would be less ataxia and perhaps she could draw or write.*

- *If she were to consume carbohydrates and sugars, dangerous levels of lactic acid would present and increase the risk of painful and lethal metabolic **acidosis**.*

Seizures:

- *Regarding **seizures** specifically, a good day for (her) might consist of her only having a couple, whereas on a bad day, she could have upwards of 20 or more.*
- *Our biggest worry is her chance of developing life-threatening **seizures** and/or metabolic crisis. (She) is at risk for organ decline and neurological degeneration which would result in a limited life span.*

Fear of death due to these symptoms:

- *As a family, we have lived in a crisis mode for the past 20 years. Constantly worried about **death**. We have already watched her regress medically and physically and we fear that every illness will be the one that **ends her life**. Even minor illnesses can be catastrophic, so we **live all day every day in fear**.*
- *When she was 4, the hospital emergency room was a revolving door for us with recurrent fevers, loss of mental status, and acidosis; watching her go limp with a mere virus and us fearing additional severe cerebellar strokes which had left her with permanent severe ataxia. While the diagnostic tools were abundant - MRI, blood tests, muscle biopsy - the suggestions on how to help her improve were next to nothing. We were told to **prepare for her to die**.*
- *Every drive, every single drive, would result in a choking event where we would frantically pull over, rip her out of her car seat and suction her airway. Although a choking event while driving is terrifying, it pales in comparison to a choking event during sleep. **I live in constant fear** that I won't wake up for the next one.*

Existing Treatments for PDCD

No FDA-approved treatment exists for PDCD. Current options for symptom management and general supportive care mainly focus on a ketogenic diet, often with physical or occupational therapy to help with muscle function. When asked what efforts patients or caregivers are taking to improve quality of life, survey results showed the most frequently utilized options as a ketogenic diet (79%), physical therapy (67%), and the use of adaptive mobility devices (67%). Every participant on the session noted the importance of diet - often with a caveat, that while helpful, it was not a cure.

Ketogenic diet:

- *Currently, her lactic acid levels are managed by the **ketogenic diet** but there is currently no cure for this disease.*
- *The **ketogenic diet** remains the main treatment for the disease to bypass the citric acid cycle to provide cellular energy. But it is not enough. We also treat her symptomatically; sodium bicarbonate to fend off acidosis, a cocktail of supplements for bone health, and fat processing, narcotics and muscle relaxers for pain and spasm. We are grateful for the symptomatic treatments we have. But every day we see our daughter slipping away without better treatments and modalities for PDCD.*
- *Even with the therapeutic **ketogenic diet**, we still see (her) struggle with her energy levels.*
- *The **ketogenic diet** has had a significant impact as the change we observed was almost immediate, but it does not address the cognitive deficit or the mental health issues.*
- *The **ketogenic diet** has essentially saved her life; however, it is not without challenges. She has severe osteoporosis, in part due to the diet. She has had 52 orthopedic surgeries and several fractured bones. She has endured hundreds of hospitalizations for respiratory illness because she is not always strong enough to fend off even minor viruses.*

Due to the positive impact a ketogenic diet can have on outcomes, several participants brought up adjacent regulatory issues, such as the need for better carbohydrate labeling and the desire to add PDCD to newborn screenings.

Sugar-free labeling and medicine:

- *The only treatment we have right now for PDCD is a ketogenic diet. Thankfully, I am fairly intelligent and know how to not just read but **understand nutrition labels**. But there comes a point where even understanding them is not enough. Now, we have to question them too. My son's daily allotment is 10g of carbohydrates. As if that is not hard enough, due to a loophole in the FDA rounding rules, companies ... can make false claims that they are a sugar-free candy and have 0g of carbs.*
- *As you know by now, sugar and carbohydrates are toxic to people with PDCD, but **most medications have carbohydrates in them**. Access to acetaminophen and NSAIDs (non-steroidal anti-inflammatories) that do not contain sugar is limited to suppositories or crushing adult pills and finding safe OTC medications for cough,*

*congestion and constipation are almost impossible. It would be very helpful to have access to **more carb-free multivitamins, OTC medications, and prescription medications.***

Adding PDCD to newborn screening:

- *We feel gene therapy and early diagnosis through **newborn screening** are the promising routes to give any child with PDCD a fighting chance.*
- *Early implementation of the ketogenic diet is of the utmost importance for PDCD patients, and for the first ten months of her life, Piper's regular diet could have been progressing her disease. This could have been entirely avoided if PDCD was included on the **newborn screening.***

Desired outcomes for potential treatments

When asked "Which outcomes would be meaningful to you for a possible drug treatment?" via survey, patients and caregivers prioritized gains in developmental/cognitive ability (91%) and gains in function such as energy, strength, mobility, and dexterity (91%) as the top two outcomes, followed by slowing/stopping the progression of the disease (81%) and prolonging life (79%). Participants on the session were asked a similar question, largely mirroring the survey, with the addition of improving diet flexibility.

Improve energy/muscle tone:

- *She has weak core strength. So that limits where she can be. Playing or doing a learning activity. Anything that **improves muscle and fatigue.** They look like they just ran a mile.*
- *In an ideal world, treatments for PDCD would **improve energy output**, increase the PDCD function and inhibit cellular death. Treatments focused on quality AND quantity of life, that would **create stronger muscles for tone, speaking, eating, and breathing.***
- *It is important to recognize that a successful treatment even with small incremental improvements in the devastating symptoms of PDCD could have profound benefits later in the course of this disease. An **incremental improvement with (her) muscle weakness** during childhood and infancy could have improved her ability to weight bear, perhaps avoid severe hip dysplasia, avoid heaps of durable medical equipment, and perhaps even walk.*

Slow/stop the disease's progression:

- Anything that can **stop the progression of the disease**. Stopping or slowing organ decline or nerve deceleration.
- Get her through the **progression and degradation of the disease**.
- Our priority would be **slowing or stopping the progression of symptoms**.

Improve diet flexibility:

- Something that would **allow more carbs**. (His) daily limit is 10 grams. Almost impossible. He's mild, he's doing great. But it's also not practical to sustain. Something that will **allow his body to process some carbohydrates**.
- **Flexibility on what we could feed** our daughter. Every day we struggle with her metabolism.
- It's not just a want to **consume carbohydrates**. Carbs become scary and life-threatening. Anything that would provide energy to the cells. To provide muscle tone, increase energy to all the muscles and organs. Muscle strength to breath.

Openness and risk assessment regarding new treatments

Given the poor outcomes associated with the disease, not surprisingly, participants were open to trying a variety of treatment options - even those with some risk.

- We feel **gene therapy** and early diagnosis through newborn screening are the promising routes to give any child with PDCD a fighting chance. Our hope for gene therapy is to give her body a chance to eat a more normal and sustainable diet and help eliminate the scary degenerative end of life situation we may be facing. We are also hopeful for **small molecule therapy** to also bridge the gap, for example, a trial for therapeutic treatments while we are in the early phases of gene therapy research.
- During the Covid pandemic, the FDA granted emergency authorization for treatments and vaccines because it was the right thing to do. PDCD is our emergency. I would like to see **rapid approval of repurposed FDA approved medication to treat PDCD** as well as **streamlined approval of studies for novel**,

promising therapies and therapeutics. Our loved ones do not have a lifetime to wait. As a family, we would be willing to **assume a moderate amount of risk** when it comes to this process. When a slow and painful death is the only other option, the **risk associated with new treatments becomes miniscule.**

- *Although my son and I are part of the Natural History study for PDCD, we unfortunately missed the deadline for (him) to participate in a clinical trial offered to him by one week. It was then suggested he try a few **new experimental treatments** when available which we are so excited about given there are no treatments available for PDCD. But do you know who was not offered those treatments? Me, the adult. I am also willing to **trial small molecule therapies** and would **allow gene therapy to be performed on me.** I also know I am not alone. There are more symptomatic moms and adults with PDCD just like me who are **willing to go to extreme lengths** to find treatments for ourselves and our children.*
- *We understand that the best chance at extending lifespan and improving quality of life for patients is through **gene therapy and small molecule therapy.** We did have the opportunity to participate in a clinical trial but declined due to travel requirements, with the closest hospital being an 11-hour drive. I am also a parent board member for a PDCD foundation fighting to give our kids a chance at a better life through gene therapy research. As her parents, we struggle with protecting her in a bubble but also wanting to give her fun childhood experiences. Managing this fear weighs on our hearts daily. The reality of our situation is that eventually degradation of her body and the progression of the disease will take (her) life.*
- *My husband and I are **willing to accept risk** because we are out of time. PDCD is a progressive disease and every day we wait on new treatments could mean more damage or loss of function that she will not get back. We are **willing to take risks** because (she) deserves a chance at a future. A future filled with less pain and a little more joy.*

FDA divisions represented

Office of the Commissioner (OC) - 2 offices

- OC/OCPP/PAS - Office of Clinical Policy and Programs/Patient Affairs Staff (*organizer*)
- OC/OCPP/OPT - Office of Clinical Policy and Programs/Office of Pediatric Therapeutics

Center for Biologics Evaluation and Research (CBER) - 3 offices/divisions

- CBER/OCD - Office of the Center Director
- CBER/OCD/PS - Office of the Center Director/Policy Staff
- CBER/OTP/OCE/DCEGM/GMB1 - Office of Therapeutic Products/Office of Clinical Evaluation/Division of Clinical Evaluation General Medicine/General Medicine Branch 1

Center for Drug Evaluation and Research (CDER) - 6 offices/divisions

- CDER/OND/ODES/DBIRBD - Office of New Drugs/Office of Drug Evaluation Sciences/Division of Biomedical Informatics, Research, and Biomarker Development
- CDER/OND/ODES/DCOA -Office of New Drugs/Office of Drug Evaluation Science/Division of Clinical Outcome Assessment
- CDER/OND/ON/DNII - Office of New Drugs/Office of Neuroscience /Division of Neurology II
- CDER/OND/ORDPURM/DRDMG -Office of New Drugs/Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine/Division of Rare Diseases and Medical Genetics
- CDER/OTS/OB/DBIV - Office of Translational Sciences/Office of Biostatistics/Division of Biometrics IV
- CDER/OTS/OCP - Office of Translational Sciences/Office of Clinical Pharmacology

Partner organizations

Partner organizations that helped identify and prepare patient community participants include:

United Mitochondrial Disease Foundation

For more than 25 years, the United Mitochondrial Disease Foundation (UMDF) has built a global network of patients, researchers, clinicians, institutions, and industry partners dedicated to fighting mitochondrial disease. Together with the mito community, UMDF is committed to a mission of funding the best science no matter where it is found in the world while at the same time providing critical education, advocacy, and support-focused programs and services to patient families. Learn more at umdf.org.

MitoAction

Since 2005, MitoAction has transformed the lives of families affected by mitochondrial disease. Our mission is to improve the quality of life for children, adults, and families living with mitochondrial disease through support, education, outreach, advocacy, clinical research initiatives, and granting wishes for children affected by mitochondrial disease. Committed to making the largest impact possible, MitoAction serves individuals in the U.S. and worldwide through support, education,

outreach, advocacy, and clinical research initiatives. The programs and services MitoAction provides continue to be a lifeline for families impacted by mitochondrial disease. Learn more at mitoaction.org.

The Elizabeth Watt PDCD Research Fund

Through outreach, philanthropy and advocacy, The Elizabeth Watt PDCD Research Fund will support research for Pyruvate Dehydrogenase Complex Deficiency, by promoting small molecule research, advocating for adding PDCD to the Newborn Screening Test, providing essential education to caregivers, and travel grants to families seeking specialized PDCD care. Learn more at pdcdresearchfund.com.

Hope for PDCD

Hope for PDCD was founded in 2022 with an urgent mission: to cure Pyruvate Dehydrogenase Complex Deficiency. Hope for PDCD's core values are: 1) to empower PDCD patients and families, 2) to promote solidarity among the PDCD community and 3) to build a better future for PDCD. All financial gifts are invested wisely and 100% of every dollar donated goes to research and advocacy efforts for PDCD. Hope for PDCD has quickly grown into a collective of volunteer parent and patient board members, scientific advisors, and industry partners. Hope for PDCD aims to fund a multi-million-dollar research project into AAV9 gene replacement therapy for PDHA1 mutations while pursuing equitable access to diagnosis, care and treatments for PDCD patients. Find out more at hopeforpdcd.org.

Disclaimer

Discussions in FDA Patient Listening Sessions are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report reflects the United Mitochondrial Disease Foundation's and MitoAction's account of the perspectives of patients and caregivers who participated in the Patient Listening Session with the FDA. To the extent possible, the terms used in this summary to describe specific manifestations of PDCD, health effects and impacts, and treatment experiences, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire PDCD patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.