# Unlock CTX Patient-Focused Drug Development Meeting

September 14, 2021
TRANSCRIPT

Kim McCleary (00:16:44):

Hello and welcome to the Unlock CTX Patient-Focused Drug Development Meeting on Cerebrotendinous Xanthomatosis. My name is Kim McCleary and I'll be moderating today's meeting along with Neel Odedara. To lead off today's meeting, we'll receive some welcome and introductory remarks from Robert Rauner, President of the United Leukodystrophy Foundation, the organization that has convened today's meeting on behalf of the CTX community. Bob, it's great to see you. We look forward to your welcome.

Robert Rauner (00:17:15):

Thank you, Kim. Hello again, my name is Bob Rauner. It's usually what I get called by. So sometimes I go official when I'm doing something like this. So I am the President of the United Leukodystrophy Foundation. First of all, I want to welcome and thank all of the members of the Food and Drug Administration that are present here today to hear the stories of our CTX families. I'm also really excited to welcome all of our family participants who have taken their time to present to you today. We also have many family members that are on this virtual meeting as well. And so I want to also welcome the rest of our virtual guests and thank them for attending so they can learn more about CTX. United Leukodystrophy Foundation in 2007 brought on our first board member that had a family member with CTX. That's really when we began to learn more about CTX and started efforts to create opportunities for increasing knowledge about CTX.

Robert Rauner (00:18:19):

We gave a grant to Dr. Andrea DeBarber to help her in her research work. We've held CTX specific meetings at our conferences every year since that point in time. And we also hosted an international meeting to discuss adding CTX to the Recommended Uniform Screening Panel. We also then supported the effort to bring the CTX nomination to the Advisory Committee on Heritable Disorders in Newborns and Children in November of 2018. Over the past year, we've been working very closely with the CTX families to host this patient-focused drug development meeting. And we've also led the way to help them form a nonprofit called CTX Alliance. We also want to acknowledge the following organizations that have been our partners in this effort.

Robert Rauner (00:19:10):

Alex, Leukodystrophy Charity, the CTX Alliance, the European Leukodystrophies Association, Hunter's Hope Foundation, Leukodystrophy Australia, the Leukodystrophy Resource and Research Organization, and the Spanish CTX Association. As you can see with those list of names, we have a very large international contingent of supporters that are working for the cures for CTX across the globe. Next we want to especially thank our generous sponsors, Travere Therapeutics and Leadiant Biosciences. Without them, we probably would not be here today. So we thank them for their support. And I want to introduce you back to Kim McCleary, the Founder and CEO of Kith Collective . And especially I want to thank her and Sam Mayberry for all the work that they did to make this patient-focused drug development meeting the success that it will be. Kim's going to be now leading you through the CTX via patient-focused drug development meeting. So back to Kim and Neel in the studio.

Kim McCleary (00:20:19):

Thank you so much, Bob. We really appreciate your opening this meeting and kicking us off today. It's really a tremendous pleasure and honor to be with the CTX community to facilitate this meeting that I'm confident will lead to a better understanding of what it's like to live with CTX and the range of experiences and expectations that people affected by CTX have to share with FDA, life science companies, researchers, and others. I've had the opportunity to collaborate with FDA for nearly a decade since patient-focused drug development came into existence in 2012 to create forums like this one for patient and family perspectives to inform medical product development and decision making. And I can tell you from that experience that the CTX story has several unique features that we'll hear about today. And one thing that I've learned from community members is how few forums there have been for CTX patients and families to come together and share their experiences.

Kim McCleary (00:21:16):

I hope this meeting will be a catalyst for connection and community building, and that your voices will gain strength through unity. I'm inspired by the resolve and resiliency with which you lead your lives and know how important those qualities are to successful advocacy for change. And with that, allow me to introduce my co-host Neel Odedara. Neel's profession as a consultant to life science companies gives him insight in how meetings like this one have the potential to improve drug development. Perhaps more importantly, Neel is a community member and he played a role and his sister, Sangna, who we will hear from shortly getting diagnosed with CTX. He's also a founding member of the CTX Alliance. And I want to thank you, Neel, for taking time away from your professional and family responsibilities to join me here in the studio today and add to this discussion.

Neel Odedara (00:22:10):

Thank you, Kim. Thank you for having me. My name is Neel Odedara. And three years ago, my sister Sangna was diagnosed with CTX. Since her diagnosis, it's had a profound impact on my family, and it seems like every day we're navigating the unknown implications of her CTX. With the help of my family, our physicians, and many in the CTX community, every day we learn more about what we can, and most importantly, cannot anticipate. It's our hope that today's discussion will be an engine to drive further understanding of CTX. And I'd like to thank the ULF, Sam and Kim with The Kith Collective , the CTX Alliance, and all the various participants here today for starting us on that journey.

Kim McCleary (00:22:57):

Great. Thank you so much, Neel. So pleased you can be here. Our agenda for today can be found in the program booklet available at ctxresource.org/unlockctx, the very same page where you're viewing today's meeting. And you'll see that the meeting is divided into two main sessions. The first of which is dedicated to understanding the diagnosis and the diagnostic journey, the symptoms that present across the lifespan, and those that impact daily function, port of therapies, and all the things that all of you do to obtain the best quality of life and function possible. We'll also talk about the unmet needs of the community and what aspirations you have for additional treatments. For each of these sessions, we'll start with a panel of community members who have prerecorded brief descriptions of their experiences that are relevant to those session topics. And then we'll have a discussion where we'll bring in members of the community live, who are prepared to kind of get us started.

Kim McCleary (00:23:57):

We'll also have opportunities for community members to participate by calling in, and we'll put a phone number up on the screen that you can use to join the conversation. There's also a comment form on the same page where you're watching today's meeting. And the comment period will be open for the next month. So if something comes to you later in the day or tomorrow as you're thinking back on this meeting, please send it in. We can make all good use of that for the voice of the patient report. We'll also be doing some polling questions, and Neel will lead us through those in just a few minutes. We know these four hours are going to fly by. It seems like a long time, but it's going quickly already. So please know that anything or anyone that we can't get to during this live session will be captured in the voice of the patient report.

Kim McCleary (00:24:46):

Also, if you need to step away at any time during the meeting, the recording will actually be live as soon as the live stream ends today. So you'll be able to go back and listen to any parts that you might have to miss. As you can see in the agenda, each of the main sessions includes one talk by an invited speaker to help just ground the conversation today. And we'll start that presentation next with Dr. Barton Duell, who's a Professor of Medicine at Oregon Health and Science University joining us live from Portland. And Dr. Duell will provide an overview of the diagnosis and clinical presentation as he sees it as both a physician and a researcher very familiar with CTX. And as we spoke with many of you about your CTX journeys and preparation for today, we heard how important to some of you Dr. Duell's care and counsel was across your CTX journeys. So welcome, Dr. Duell. We're pleased to have you here from Portland. And I'll turn it over to you now.

P. Barton Duell, MD (00:25:50):

Well, thank you very much, Kim. It's really a great honor to be invited to participate in this program. So I thank the organizers for allowing me to speak to all of you about cerebrotendinous xanthomatosis. I've been interacting with patients with CTX for about 30 years. So it's something that I have a lot of experience with. But one thing I'd like to point out at the start is that every patient's journey with this is very different as you'll hear from the patient panels. But for some and perhaps for many, they feel alone, afraid. There's just so many unknowns when they find out they have CTX. So forums like this are excellent for helping spread information and help people really have a better understanding of what's going on with their condition. So the next slide shows my disclosures as indicated there. And we'll go to the next slide and just jump right in with the presenting symptoms of CTX.

P. Barton Duell, MD (00:26:58):

The symptoms vary from one person to another. And it's important to note that there are some people who have almost no symptoms and others who have every symptom on the list as indicated here. So in infancy, patients can have diarrhea, failure to thrive, persistent hyperbilirubinemia, cataracts are really very common and might be a clue to the diagnosis when present in children, psychomotor retardation, pyramidal and cerebellar signs as well. The next slide shows the symptom complex for adult patients. And there's a continuum here as you'll see in the next slide. But in adulthood, neurologic dysfunction becomes more apparent, which may include ataxia and spasticity. Intellectual disability/dementia can actually occur. Psychiatric symptoms of various types, as indicated here, may be present. Cataracts again, as you saw before. Xanthomas of both the extensor tendons and the brain can occur. It is not a common complication, but premature arteriosclerosis and coronary artery disease may occur.

P. Barton Duell, MD (00:28:16):

The diarrhea sometimes is self-limited and gets better. But for some adults, it continues. Seizures can occur in relation to the brain injury. And then, osteoporosis as well. And I emphasize again that not everybody gets every one of these symptoms and some may have only one. The next slide shows the time course of progression of symptoms. And I won't go through each of these in detail, but the way this is laid out is the time scale is on the age as shown on this axis. And then here shows the percentage of patients who have each symptom. And as these progress over time, the prevalence of each one of these gets worse. And you can see that some of the things like the dementia or the neurological complications tend to become more prominent once people get into their twenties and thirties. The next slide shows the biochemistry and genetics of the disorder.

P. Barton Duell, MD (00:29:31):

So it's a recessive condition, which means that to end up with this, you need to inherit a polymorphism or sometimes referred to as the variant from mom and one from dad, and the two together in this gene called CYP27A1 will cause deficiency of the enzyme sterol 27-hydroxylase, which is important for production of bile acids. Defects in the function of that enzyme, the sterol 27-hydroxylase cause a block in bile acid synthesis resulting in accumulation in the blood of cholestanol, both in the plasma, and then it goes into body tissues as well. There are a number of other compounds that kind of accumulating the blood and urine as well that are useful for diagnostic testing. Xanthomas of both extensor tendons and the brain can develop, as you heard earlier. And then it's a little bit complicated biochemistry and cell biology, but abnormal sterol sensing results due to the defects in this enzyme and that causes or induces the arterial cells to accumulate cholesterol and other sterols that lead to arteriosclerosis.

P. Barton Duell, MD (00:30:55):

Now the next slide shows characteristic cataract. Maybe you're not that interested in it, but there's a kind of a stippling in the background of the lens that contributes to the cataract. This is a very characteristic appearance in patients who have cerebrotendinous xanthomatosis. And typically this occurs bilaterally just because patients have systemic exposure to the high levels of cholestanol. The next slide shows examples of tendon xanthomas. And as I indicated earlier, not everyone gets these, but those who do have them can have quite dramatic tendon xanthomas. They can even occur in the hands or the knuckles and be quite large. They usually are painless, but depending on where they are and how much pressure there is, ones in this area for example, can become inflamed and painful sometimes. The next slide shows an example of xanthomas in the brain. And many of you are not familiar with looking at MRI images, but here's the nose in the front.

P. Barton Duell, MD (00:32:13):

These are the eyeballs. Back here is the cerebellum. And this kind of [inaudible 00:32:20] is an abnormal tissue present in the cerebellum. And this is a case of a xanthoma that then interferes with cerebellar function. And the cerebellum is important for controlling motion. So people who have cerebellar injury or damage end up with what we call ataxia, the inability to move smoothly. The next slide shows an example of another complication, actually in one of my patients, bone fracture. In this case, not due to osteoporosis, most likely traumatic injury, but bone fractures can occur due to bone loss. Next slide goes on to some summary of the clinical features of a case series we put together, 43 cases of CTX. And one thing to note is that the mean age of diagnosis was 32 years. A point that you'll hear over and over again is that early diagnosis is very important and early treatment is important to prevent complications.

P. Barton Duell, MD (00:33:35):

And the neurologic damage that occurs, it may be reversible to some extent, but especially in older adults, the amount of reversibility is often quite limited. So early diagnosis is key, age 32 years is not early. We want to diagnose these patients when they're children and initiate treatment before major complications have occurred. Diarrhea was present in more than half. Cognitive impairment was present in three-fourths. Premature cataracts were seen in the majority, about 70%. Again, these are mostly adults. So 77% actually had tendon xanthomas. And I would just add that these are often quite small and it may be something apparent only to your physician. Not all physicians are comfortable diagnosing tendon xanthomas. Neurologic disease was seen in the majority of patients. And then early ASCVD referring to atherosclerosis was seen in about 7% of patients. Next slide shows the prevalence of the condition. So the CTX, of course, is in the orphan disease category, meaning it's quite rare and it...

PART 1 OF 7 ENDS [00:35:04]

P. Barton Duell, MD (00:35:03):

... meaning it's quite rare. And the estimated prevalence isn't quite clear and it may vary in different parts of the world, but is thought to be in the range of three to five individuals per 100,000 people in the world. It's much more common in some groups where there's a founder effect such as among the Druze where the prevalence may be astoundingly 0.2% and in Sephardic Jews as well.

P. Barton Duell, MD (00:35:32):

In another analysis, looking at 208,000 patients or subjects who did not have sitosterolemia or familial hypercholesterolemia, the prevalence was 3.4 per 100.000. So right in line with the number I gave you earlier.

P. Barton Duell, MD (00:35:53):

And then an important finding published a couple of years ago is that among individuals with childhood onset of bilateral cataracts, 3 out of 170 that's 1.8% were found to have CTX. So this is a 500 fold increase in prevalence compared to the general population.

P. Barton Duell, MD (00:36:16):

So this will not pick up everybody with CTX, but it suggests that this is a very important clue, the presence of bilateral cataracts in childhood to screen for CTX. And one of the patients I see was actually identified for this reason, his ophthalmologists said, "Hey, you're young, you have cataracts, let's test." And lo and behold, that brought up the diagnosis.

P. Barton Duell, MD (00:36:47):

The next slide shows the treatment, or I'm sorry, shows the diagnosis. And then we'll go to the treatment. And the primary diagnostic tool is identification of elevated levels of the cholesterol in plasma. In addition, measurement of urinary bile alcohols is a very sensitive marker for CTX. The bile alcohols are breakdown products of cholestanol and other things that accumulate in the liver and in the blood, in this condition. For dried blood spot testing, Dr. Barbara, whose name you heard earlier, who I worked together in the sterile lab at our institution developed that technique for measuring so-called 7 alpha, 12 alpha C4 in dried blood spots.

P. Barton Duell, MD (00:37:41):

And this opens the door to doing newborn screening. And as you heard from Bob Griner, the effort is still underway to try to get that implemented to do newborn screening for CTX. And then the diagnosis can be confirmed by genotyping, sequencing the set 27A1 gene. And in some cases this is merely confirmatory. In other cases where the details are a little less clear, it can provide a diagnosis in milder cases that is with milder biochemical defects.

P. Barton Duell, MD (00:38:21):

The next slide then shows the treatment. And the standard treatment is use of CDCA, which is chenodeoxycholic acid. This is a normal bile acid that isn't present in people who do not have CTX, but is deficient in CTX. The dosing in adults is given three times a day with meals, usually 250 milligrams. And in kids, we do an age-based or weight-based dosing five milligrams per kilogram, also three times a day if possible.

P. Barton Duell, MD (00:38:58):

As you've heard earlier, early treatment is very important just because reversal of the disease may be limited. And I'd like to add a side note and this is part of the point of presenting to the FDA today is that chenodeoxycholic acid is actually FDA approved, but it's for dissolution of gallstones. And it's actually not used that much for gallstones. The primary use is for CTX. And so when we use this medication, the CDCA for treatment of CTX, technically it's kind of a off label. And the hope is to ultimately have the FDA approve this just because it is the standard of care that's a recognized worldwide.

P. Barton Duell, MD (00:39:50):

Colac acid is approved for CTX, but it is really the wrong medication for CTX because it is not as effective at suppressing the biochemical pathways that are abnormal in this condition.

P. Barton Duell, MD (00:40:07):

So the next slide goes to additional treatments and these are tailored specifically to the conditions affecting the patient. So of course, if cataracts are present and they're abnormally affecting vision then cataract surgery would be indicated. If needed, this is not standard treatment, for those patients who need it antidepressants or antianxiety, medications are helpful.

P. Barton Duell, MD (00:40:35):

If there are muscle spasms occurring, Baclofen or muscle relaxants may be helpful. Patients may need physical therapy, speech therapy, a treatment to either prevent or manage osteoporosis or heart disease may be indicated as well.

P. Barton Duell, MD (00:40:54):

And then general preventive health measures are important as well, which include healthy dietary habits, regular physical activity, of course not smoking. And then managing all of the other things that come up. Now, it's not shown on this slide, but as is true for almost all rare diseases, this is a family issue. So we don't treat just the patient. We have to manage the entire family because it has an impact on everyone. And that will come out in more detail through the patient panels that you will hear.

P. Barton Duell, MD (00:41:32):

The next slide shows a summary of what I've talked about. So CTX is a rare condition caused by Biallelic mutations in the gene CYP27A1. The consequences are related to decreased levels of bile acids. This leads to increase levels of cholestanol and tissues and other metabolites that make the tissues not happy.

P. Barton Duell, MD (00:42:02):

If untreated can be a progressive, debilitating neurologic condition. It can lead to xanthomas and the tendons and the brain. Diarrhea is a common symptom that sometimes persist into adulthood, but is reversible with treatment with chenodeoxycholic acid. Cataracts, I mentioned might be a helpful sign to facilitate early diagnosis.

P. Barton Duell, MD (00:42:28):

And then in the untreated state osteoporosis and atherosclerosis can occur. And I can't emphasize it enough that early diagnosis and treatment is essential.

P. Barton Duell, MD (00:42:41):

So with that, I want to thank all of you again, the organizers for inviting me to be part of this meeting. And it's truly an honor to share in this proceeding. And the most important part of this program is going to be the patient stories and hear it directly from them as to how this condition affects everyone, including the whole family. So thank you again for your attention.

Kim McCleary (00:43:12):

Thank you so much, Dr. Duell for your dedication to caring for CTX patients, for your research into better understanding the disorder and providing that excellent overview that will lay a very firm foundation for patients and family members to build on throughout this session.

Kim McCleary (00:43:31):

And just as you said, we will hear from them directly, but I think you'll hear a lot of common themes based on the presentation that you just gave. So thanks so much for joining us.

Kim McCleary (00:43:44):

I'm going to turn now to Nell and he's going to get our polling started so that we can hear from participants all across the viewing audience today and get you involved in this conversation. So Nell over.

Neel Odedara (00:43:57):

Great. Thank you, Kim. Thank you again, Dr. Duell for that comprehensive presentation. So as Kim mentioned, we have a number of polls that we'll be conducting through the discussion today. To access the polls that we had asked that you all visit the website pollev that's E as in echo, V as in victory.com forward slash CTX PFDD that's pollev.com/ctxpfdd.

Neel Odedara (00:44:27):

And one thing I would note is that we'll be going through a number of polls during the course of the discussion today, if you want to just keep that tab open it'll refresh so that you'll be able to participate in

the polls as they proceed. But you should be able to see the first question coming up now, which is regarding your primary relationship to CTX.

Neel Odedara (00:44:49):

So this is a poll question that is open to anyone who's participating today. You'll see some of the options, whether you're a person living with CTX, a family member, healthcare, professional, or researcher, whether you work for a life sciences company or a regulator or an advocate.

Neel Odedara (00:45:08):

And finally, we do have column G for other. So it seems like we have just, as we're watching some of the live results come in, I'm glad to see that it looks like we have a lot of robust participation and quite a few folks joining from the life sciences industry.

Neel Odedara (00:45:25):

A number of individuals who have family members with CTX and the individuals who are living with CTX as well. I'm happy to see actually we've got a diverse spread across the spectrum. We have potential participants.

Neel Odedara (00:45:43):

Great. And so, as we've seen the numbers come in, it looks like we're seeing about roughly 50% of folks are joining from life sciences companies, about 30% are those who have a family member living with CTX and also a few individuals who are living with CTX themselves.

Neel Odedara (00:46:06):

Great. So I think the final numbers are coming in here about one third of our participants they're living with CTX or who have a family member about half joining us from industry. And it looks like some solid numbers from both the regulatory and advocacy.

Neel Odedara (00:46:26):

Great, great. So I think now we can move on to our next question, our next polling question, which is where do you live? And you see, of course, we've got strong representation across US time zones here, Central Time, Eastern Time, Mountain Pacific.

Neel Odedara (00:46:46):

We're also actually very excited to see, we have a number of folks participating from other parts of the globe. It looks like about 30% are joining from Europe. We do appreciate the odd hours in Australia and in Asia. So we're very glad that this will be available offline as soon as the session today is over for those participants.

Neel Odedara (00:47:10):

We know we had comments from other parts of the globe float in as well. But as folks are filling out the poll. It looks like we're seeing roughly half of our participants are coming from the Eastern Time Zone with little less than a third coming from the Pacific Time Zone and happy to see about one fifth coming from Europe. So we thank you all. Actually, as I say more.

Kim McCleary (00:47:34):

[inaudible 00:47:34].

Neel Odedara (00:47:34):

Yeah. So as I say, especially appreciate you joining from all different time zones at all hours of the day and really helping to give a voice to the CTX community as we proceed through this discussion. Great.

Kim McCleary (00:47:54):

So now that we have an idea of who is with us today, let's get started. In the setting of the PFDD meeting I want to state firmly that the individuals living with CTX and their family members are the experts in the discussions we'll have today.

Kim McCleary (00:48:11):

So for that group within our audience that is personally connected to CTX, please hear that and take it to heart as we invite your comments and perspectives.

Kim McCleary (00:48:24):

We'll now move into our first session, which is dedicated to better understanding what it's like to live with CTX, including the challenges of getting an appropriate medical attention and diagnosis, the symptoms that appear, and how CTX affects activities of daily living, long-term function and the well-being for both the patient and his or her family.

Kim McCleary (00:48:45):

And as we prepare to listen to the prerecorded statements and then engage with community members in discussion, I want to honor and recognize the courage in being asked to recall and relive difficult experiences and memories.

Kim McCleary (00:48:59):

Each person deserves our respect and compassion for all they have lost to CTX and the bravery it takes to speak in a public forum like this. And I know many of us are missing out on the fellowship of being together in person, but we also appreciate the convenience of the virtual format that enables people from around the globe, as we've just seen to participate. And we appreciate our speakers inviting us into their homes for these brief glimpses into their lives.

Kim McCleary (00:49:27):

So let's hear now from John Wolf, who many know and consider to be the, kind of the godfather of CTX advocacy. And John speaks on behalf of his daughter, Ashley, and will be followed by Sangna and Sue Stewart who will speak on behalf of her son, Eric.

John Wolf (00:49:49):

Good morning. My name is John Wolf and I live in Portland, Oregon. I am pleased to be leading off this Patient Focused Drug Development meeting on CTX. I want to thank all of the individuals involved in coordinating this meeting and to say, thanks for allowing me to participate.

John Wolf (00:50:03):

I've been involved in raising awareness and advocacy for CTX since my daughter, Ashley was diagnosed in 2004. Over the past 17 years we have seen some progress, but as you'll hear from other community members today, there are still many needs. So we are hopeful today's meeting will bring even more attention and progress to our efforts.

John Wolf (00:50:23):

Allow me to return to the beginning of our journey with a description of how Ashley's symptoms first affected her life and our family, what it took to get her diagnosed and how she's doing today.

John Wolf (00:50:33):

I will tell you upfront that we are among the fortunate ones. Looking back Ashley exhibited one of the cataract signs of CTX from birth chronic diarrhea. While it can sound trivial caring for her as an infant and toddler was very challenging.

John Wolf (00:50:47):

We changed a lot of diapers and it became even more complicated when she was potty trained. It was especially difficult when traveling and necessitated a lot of deliberate planning, requiring that we are aware of the nearest bathroom and making extra stops. Our pediatrician reassured that she would grow out of it. When she didn't we consulted specialists. The first one who examined her didn't believe that Ashley had diarrhea episodes up to eight times a day. Eventually we found a GI doctor who ran tests for things like celiac sprue, Crohn's disease and others. Those came back negative. However, and the doctor, again, to turn to the possibility that we were exaggerating.

John Wolf (00:51:23):

Eventually he provided a generic diagnosis of irritable bowel syndrome. And we were sent home with a giant bottle of anti-diarrhea medication Loperimide, which worked for a short while and eventually stop working entirely even after the dosage was increased.

John Wolf (00:51:39):

We tried changing her diet and looked into the possibility of allergies, but nothing helped. Halfway through her first grade school year, her teacher notify us that Ashley was having issues paying attention and retaining what she had learned. This was a shock to us because it was in stark contrast to her development as a toddler when she hit developmental milestones early. At first, we had difficulty accepting it, but then we came to notice that too, and recognize this was a new reality for her. We took her to see a psychologist for testing, but no definitive diagnosis was made and no therapy was prescribed. We accepted the fact that she might always need help in school.

John Wolf (00:52:17):

In December of 2004 when she was age 10, we noticed that Ashley was suddenly holding her books closer to her face when she read and she sat closer to the TV than before. This was especially alarming because at the beginning of that school year she had been tested and had 20/20 vision. Very quickly we took her to the local optometrist to test, he tested her and told us that she was now 2100 and had cataracts in both of her eyes at age 10.

John Wolf (00:52:44):

We were advised to see an ophthalmologist and through a referral from a friend, we made an appointment with one across town who confirmed the diagnosis of cataracts. In addition to the thorough exam, he took a medical history and told us that Ashley did not fit the profile for any of the common causes of juvenile cataracts.

John Wolf (00:52:59):

We were very fortunate. However, he was curious enough to dig deeper into our background, which led him to suggest that she might have a metabolic disorder. He immediately referred us to a genetic specialist. He also performed a surgery to correct her cataracts. Despite an initial complication that affected the wound healing after the first time it was operated on, she made a full recovery and returned to 2020 vision with the help of light focal lenses.

John Wolf (00:53:24):

We met with the genetic specialist right away upon referral. After some initial inconclusive test and one that presented the possibility Ashley might have Smith Lemli Opitz Syndrome two months and another test later, we received a confirmed diagnosis of CTX. Through our own new search during the wait for the test results we established contact with Dr. Gerald Salem, who tested some of the samples that the geneticists had collected from Ashley.

John Wolf (00:53:48):

For a decade, we had been fighting this battle to understanding the source of Ashley's difficulties. The cataracts were a blessing in disguise because they led to her getting a correct diagnosis before CTX progressed into a debilitating condition and had also connected us to the world's leading expert on CTX.

John Wolf (00:54:05):

We also had our son Jacob tested for suspected [inaudible 00:54:08] carrier for the genetic mutation that causes CTX. We finally saw a light at the end of the dark tunnel.

John Wolf (00:54:15):

Ashley was quickly enrolled in Dr. Salem's clinical trial CDC therapy, which was not otherwise available in the United States at the time. Over the course of the first year, the chronic diarrhea improved and she began to do markedly better in school. She gained 70 pounds, which finally put her into a normal weight percentile. Results on her EEG were much improved compared to the EEG done before treatment started that it showed increased electrical activity and actually induced a seizure during the test. This was all positive.

John Wolf (00:54:43):

Now Ashley is 20, independently works, drives and has a three-year-old. Daughter without her diagnosis at age 10, I'm afraid I would be telling a very different story. Over the years since Ashley's diagnosis, I became involved in efforts to maintain patients access to CDCA when it was accessible only from Germany, then through a pharmacy in London, and later when it became available in the US. But change chance from one company to another. I served as a CTX representative to the United Leukodystrophy Foundation, and later joined their board of directors. We built a website featuring CTX resources and help parents and patients connect to doctors and one another.

John Wolf (00:55:19):

I participated in advocacy for newborn screening, which is a major help to our community. I feel a great sense of pride to be here today with so many members of our community and for you to hear all of our stories, hopes, aspirations, to advance treatments care, and to perhaps bolster our awareness efforts in which someday lead to a cure. Thank you. [inaudible 00:55:41].

Sangna Oderada (00:55:42):

Hi, my name is Sangna, and I want you to talk to you about CTX. I was diagnosed with CTX when I was 34 years old. Even though I learned about my CTX later on in life, it has shaped my life in a profound way that I'm still trying to understand.

Sangna Oderada (00:55:58):

When I was a baby I had frequent GI issues and my family had immigrated to the US when I was 6 years old. For as long as I can remember, I had difficulties concentrating in school. I struggled in school and my parents had to get... I struggled in school then my parents had to get help on and off over the years with various physicians. As immigrants living in a small town in rural Virginia we didn't always have access to the best care.

Sangna Oderada (00:56:34):

Instead, I saw doctors on and off over the years. I saw primary care doctors, cardiologists, psychologists, and many other specialists.

Sangna Oderada (00:56:48):

Each one had a different theory of what I had. At various points I was evaluated for marathons, scoliosis, cardiac diseases, ADHD, and thyroid issues. Finally, when no one could find anything they concluded it was nothing. My parents were told some kids just don't like school while I struggled to keep up in school. When I was in my late twenties, I was diagnosed with cataracts in my right eye. By the age of 30, I had cataract surgery in my right eye and by the age of 31 I had surgery in my left eye for cataracts. This was strange to doctors. They said that I should have this problem in my sixties. And I had it at such an early stage.

Sangna Oderada (00:57:42):

Our ophthalmologists said it was strange. The pattern went on and on until my late to mid thirties. And the whole time my family struggled. They knew something was wrong they just didn't know what. Finally by chance my brother was working on Parkinson's disease or a project at work, he thought I might have a neuromuscular disorder and got me enrolled at a study in [inaudible 00:58:18] Maryland at the NIH facility.

Sangna Oderada (00:58:23):

There I was diagnosed with CTX. The news was hard on my family, but it was a relief for me because I finally knew I had something that I could put a name to. Today I still struggled with certain symptoms like concentration, memory loss, and muscle weakness. But with my family's help, I'm looking ways to have a normal life where I can. I'm going to school again and I have a job that is flexible and not too physically demanding.

Sangna Oderada (00:58:57):

Without me knowing CTX held me back from everything. I wanted to do better in school and in life. I'm grateful for my family, for the physicians that came up with my diagnosis and my CDCA treatment. But still there's so much we need to do and understand about CTX. So people like me and people still early in their journey don't have to stumble in the same dark like I had to.

Tom Johnson (00:59:35):

Hi everybody. Thank you for the opportunity to be a part of unlocking the CTX. My name is Tom Johnson, and this is my wife, Debra Johnson. She is the CTXer. Debra was born in 1974. I'll give you a little bit of background here for context.

Tom Johnson (00:59:51):

We met in college where she was studying electrical engineering. It was love at first sight. We were engaged within a month from the day we met, married seven months later, and that was 26 years ago.

Tom Johnson (01:00:05):

Debra went on to be a [road 01:00:07] scholar, and she studied at the University of Oxford getting her master's degree there in management. She was a high flyer. Professionally, she was by age 25, the director of a telecom electronics manufacturer with 60 engineers working for her. Then we sprinkled in a couple of kids into the mix in 1998 and 2000 with our daughter and then our son. And by age 32, she was the general manager of an electronics manufacturing plant with over 600 employees.

Tom Johnson (01:00:40):

Two years later, by the age of 34, she was the president of the manufacturing company with over a hundred employees. And she loved her work and she was very, very good at her job.

Tom Johnson (01:00:52):

But in 2009 health started to decline. She had started having severe GI pain and diarrhea as well. That's when we started a search to try to figure out what's going on medically. Life changed even more drastically in February of 2010, she was hosting a meeting of executives for her company and she had a major transient ischemic attack. She got dizzy, she collapsed, she had a phagia. She was unable to speak, even though she knew what she wanted to say. They rushed her to the hospital and after spending an evening there, they really didn't have any answers. The next TIA came three days later.

Tom Johnson (01:01:37):

After that, there had been lots of doctors still with really no clear answers. And by 2011, she was unable to work. She had seen doctors across the board, including the UNC System, the Duke System, and the Cleveland Clinic. The one thing that she was on to help to relieve some of the symptoms was she was on oral steroids. That helped somewhat. That was kind of the beginning of a very long diagnostic journey.

Tom Johnson (01:02:09):

In 2011 she got an appointment with an autoimmune neurologist at the Mayo Clinic in Rochester, Minnesota. Autoimmune component had been identified with her particular condition. After that appointment we had many more questions than answers and that one appointment turned into staying there in Rochester for three weeks. During which time Debra saw 13 doctors and had a slew of diagnostic tests.

Tom Johnson (01:02:39):

At the end of that, the answer still wasn't very clear but she had a diagnosis of autoimmune encephalopathy and they switched the steroids from the oral steroids to Ivy pulse dose steroids, which did help a little bit for a while. But her condition continued to deteriorate fairly quickly.

Tom Johnson (01:03:03):

She had tachycardia, heart palpitations, chest pain. She had developed a cerebellar tremor and left sided weakness, which decreased her mobility and she was often in a power wheelchair. She had pain after every meal... Pain many times, but especially after meals. And she had extreme fatigue, both physical and mental.

Tom Johnson (01:03:25):

And she would often sleep 12 to 14 hours every day. But probably the most frightening was the cognitive decline. Here you have this brilliant woman who has lost mental clarity. Short-term memory was very difficult for her. She had difficulty with word finding, and also with word substitution.

Tom Johnson (01:03:45):

She had gotten to the point where she really couldn't read a book for not remembering the prior paragraph. And the kids would be asked multiple times a day if they had homework that afternoon, she wouldn't remember having already asked. And really Debra's biggest fear was at what point am I not me anymore?

Tom Johnson (01:04:08):

She had tried, or her doctors had tried many treatments. She failed Imuran, CellCept rituximab IVIG, cytoxin. Really, without a clear diagnosis, the doctors were out of ideas.

Tom Johnson (01:04:24):

And the fall of 2015 was a real challenging, low point for us. Debra was 41 years old. We had two teenage kids in the house. The trend of her symptoms and her function were both in steep decline. And just speaking between ourselves, we felt that she would be lucky to see the age of 45.

Tom Johnson (01:04:48):

So we resolved to make the best of it, make great memories and basically just enjoy every day with ourselves and with our family. But Debra is a fighter for slogan has been-

Debra Johnson (01:05:01):

Never give up.

Tom Johnson (01:05:01):

"Never, never, never give up." And so we started looking for clinical trials. We found one, which she got into. It was called the IDIOM study, Idiopathic Diseases of Man. Basically a genetic study where they take the data that they find and hopefully unlock potentially life-saving insights by identifying what disease may be causing the condition.

Tom Johnson (01:05:27):

And we had a massive evening, December 29th, 2015, late in the evening, way after work hours. Debra's hematologists called and said, the results of the IDIOM study are back-

Debra Johnson (01:05:40):

That was something.

Tom Johnson (01:05:41):

... we may have a diagnosis. And that was CTX. So within a couple months, Debra had started treatment on [chenodeox 01:05:50] and over the course of the next year she improved. I mean, some of the cognitive symptoms improved somewhat. And then it seemed to stabilize. They weren't progressing as rapidly. Cerebellar tremor seemed to get better. So that helped with her mobility. And-

Debra Johnson (01:06:09):

I could read a book.

Tom Johnson (01:06:11):

Yeah. She could read a book. And she felt like she had her life back, or at least it wasn't getting worse from a functional perspective very quickly.

Tom Johnson (01:06:20):

So in 2019, we celebrated her 45th birthday after our earlier fears. And every day since then is a bonus day for us. So although we continue to fight the disease every day, we have a much stronger sense of hope and optimism that we have many years remaining together. But we both feel that early diagnosis is key. It allows people to begin treatment sooner and hopefully prevents damage from occurring in the first place.

Tom Johnson (01:06:50):

And we're hopeful that unlocking CTX will be an important step towards leading to earlier diagnosis and treatment. As a notable bright spots, Storm, a service dog from Canine Companions for Independence WAS just placed here in late August with our family. He's an amazing dog and we're very happy to have him joying the family. And with that, we'll wrap up. Thank you very much for the chance to be a part of unlocking CTX.

Debra Johnson (01:07:19):

Thank you.

Susan Stewart (01:07:23):

My name is Susan Stewart and I live in Albany, Oregon. I am the mother and now legal guardian of Eric Stewart. Eric is now 30 years old and he has CTX. Eric was not correctly diagnosed or appropriately medicated for CTX until he was 16.

Susan Stewart (01:07:47):

His diagnosis came earlier than many people who have CTX, but not as early as it could have been. My pregnancy with Eric and his birth were quite normal. I brought home a happy baby who nursed well and

slept through the night at six weeks. He had a little more diarrhea than was usual, but a top pediatric gastroenterologist we consulted didn't seem too concerned about it.

Susan Stewart (01:08:16):

Initially, Eric seemed to be on the same developmental schedule as his two older half-brothers. Then when Eric was 16 months old, his babysitter commented, "I have never seen a toddler who likes to play by himself so much." That made me start paying closer attention to Eric's development.

Susan Stewart (01:08:39):

I noticed that he had a few words of speech by 11 months old, that he lost. By age two he had no words and only babbled. He babbled vowel sounds. His pediatrician did not seem overly concerned, but did refer him to an audiologist who suggested tubes in his ears.

Susan Stewart (01:08:59):

The tubes solved his ear concerns but did not resolve the developmental issues. At two and a half eric was diagnosed with a communications disorder. At three, he was diagnosed with autism, at five. He was diagnosed with a seizure disorder, Landau Kleffner Syndrome, as six he was diagnosed with a likely immune system disorder because his MRIs were showing decreased white matter and increased gray matter in his brain.

Susan Stewart (01:09:32):

Around age nine, he was identified as being intellectually disabled. At 11 he was diagnosed with bilateral cataracts. No one connected the cataracts to his other difficulties. During Eric's diagnostic journey I sought the advice of many practitioners and Eric participated in many therapies, a great burden in terms of financial expense and time for our family. Some of the therapies were scientifically based, but we tried other therapies-

PART 2 OF 7 ENDS [01:10:04]

Susan Stewart (01:10:03):

Other therapies were scientifically based, but we tried other therapies that were not based on evidence. I was desperate to help my son. I was a single mother, so all of this was on my shoulders and I needed to continue working to support all of us. By the time Eric was 16, he had totally deteriorated. He was non-verbal and mainly communicated by typing words, but not sentences on an augmentative communication device. He could not perform many activities of daily living like bathing, dressing himself or brushing his own teeth. If we went on an outing of any lengths, he required a wheelchair. His IQ was 40 on the whisk scale. Additionally, although he had previously had high energy, he began to have extremely low energy. He just sat on the floor and quietly played with his toys. At age 16 Eric was very ill. I feared, he was dying.

Susan Stewart (01:11:05):

I did a Google search using the words, cataracts and autism. I've found that disorders related to difficulties with cholesterol often had cataracts and autism occurring together. And I found one of the main facilities studying these disorders was at Oregon Health Sciences University. We lived in Oregon. So we went to OHSU where Eric received the correct diagnosis and began treatment. Since beginning

treatments, Eric has made improvements, but he remained severely impaired. He is now able to dress himself and buckle his own seatbelt, but he cannot cook for himself or bathe themself.

Susan Stewart (01:11:45):

He has more energy. In fact, after he started on treatment for CTX, some of his physical symptoms improved, but the change in his energy levels combined with long-term damage to his brain led to the start of more aggressive and self-injurious behaviors. It became very hard for me to manage him on my own, and it was harder than ever defined, paid home health workers who could manage him while I was at work, given his rambunctiousness and outbursts, it became necessary to place Eric in a full-time residential care facility. And he now lives in a group home for developmentally disabled individuals. Eric's wheelchair has been given away, but he continues to have a profound, expressive language disorder, a severe receptive language disorder and moderate to severe autism. He has Medicare and Medicaid. He receives social security, disability income, which he uses to pay for his room and board and for spending money. Additionally, the state of Oregon provides about $10,000 per month to pay for his caregivers at the group home. Eric's recent individual service plan was three fourths of an inch thick. I cannot imagine that he will ever hold a job or be able to live independently. Still as his mother and fiercest advocate, I celebrate his small achievement. At the age of 25, Eric learned to get himself a cup of water when he was thirsty. He enjoys watching children's counting videos on YouTube, playing basketball and going to the arcade where he has learned and earned the name ski-ball wizard. Eric's CTX has greatly impacted our family, including his two older half-brothers. One of them has been tested for CTX and thankfully does not have it. We know of one other family member, a half sibling on Eric's father's side, who is a CTX carrier. I hope this meeting and sharing our family's experience will spur advances that lead to earlier diagnosis, including thorough newborn screening tests and more complete treatments for all the ways that CTX can affect individuals like Eric, thank you for your time and attention.

Kim McCleary (01:14:21):

Wow. What a powerful set of testimonies that was really helping us to understand what it's like to live with CTX and to bring the lived experience to the clinical overview that Dr. Duell started us off with. You can see as he had indicated how different the journeys can be. It's really profound when you put Ashley's story next to Sangna's next to Debra's next to Eric's and just how many different factors are involved. Before we transitioned to our discussion, Nell, I want to turn it over to you for some additional polling questions and also to hear if we've had any comments come in and what we're hearing from other meeting participants.

Neel Odedara (01:15:06):

Certainly thank you, Kim. And I would say similarly, I think just watching those powerful testimonies, I want to thank everyone who was able to share their stories. One thing that struck me is that even across the wide spectrum of symptoms that we saw, the one commonality that's clear is that even mild symptoms have the inability to dramatically change the trajectory of someone's life. And I think that that's something that we're seeing as well, based on some of the comments that we're hearing that we've received from, participants. We have Priscilla in Malta mentioning how her sibling was diagnosed at an early age. We have Dwayne from Yakima mentioning that the largest challenge he has, the largest obstacle is not being able to walk every day. Every day is different, but most days are very difficult and it limits his independence every day. I think with that, I think we'd like to turn to our next polling question. Just as a reminder, if you'd like to participate in the poll, the next set of questions is open to those in the CTX communities. So family members, folks for whom they are diagnosed with CTX and the website to

participate is pollEV, E as in echo, V as in victory.com/CTXpfdd. And our next polling question is, how old were you when you were diagnosed with CTX? If you are a family member, please make sure that you answer for the oldest member of your family and the options here are if you were diagnosed under the age of two, two to 10, 11 to 20, 21 to 30, 31 to 40, 41 to 50, over the age of 50, and the I don't know.

Neel Odedara (01:16:59):

And I think in line with what we heard from Dr. Duell earlier, the most common age of diagnosis is in the mid thirties. We're seeing right now about 40% of participants saying that is when they were diagnosed, but clearly for many patients, the symptoms may start much sooner. And it seems like even as we look across our polling results, to this point, broad spectrum, 8% or 16% diagnosed under the age of 10, about a quarter diagnosed between 10 and 20 and is in a clear majority diagnosed between 31 and 40.

Neel Odedara (01:17:43):

Great. So thank you everyone for participating in the poll. As I mentioned earlier, you do have the option. If you just keep that website open the polls will refresh with the next question. And with that in mind, I also want to take this opportunity to encourage you to call in. We do have the option. We will be taking calls during the session. And that phone number to call in is +1 703-844-3231. If you are a member of the CTX community, we would appreciate you calling in to share your thoughts, your comments, your experiences. I think every perspective helps in that number again, to call in is +1 703-844-3231. Thank you.

Neel Odedara (01:18:37):

And I believe we do have a second polling question. So just bringing that up on screen. Now our second polling question is, how long did it take to get diagnosed with CTX after symptoms appeared? If you have multiple family members with CTX, again, this is a please answer for those members with the shortest time to diagnosis. And in terms of, it seems like in terms of the options that we have available, within two years, two to five years, five to 10, 11 to 20, and more than 20 years. It seems clear here that the broad majority of our community are experiencing symptoms with between, as early as within the first two years. But it seems like the broad majority are experiencing those within five to 10 years or 11 to 20 years of diagnosis. So roughly about 66 or about 72% here, experiencing those symptoms within five to 10 or 11 to 20 years of diagnosis.

Kim McCleary (01:19:53):

And I'll bet it can be challenging to even know when symptoms start. So many people described that they were brushed off by an early encounter with a pediatrician or early in life. And maybe just didn't even connect some of those early life symptoms with the diagnosis, ultimately when they got it.

Neel Odedara (01:20:12):

Right, absolutely.

Kim McCleary (01:20:16):

Great. Well, as the polling has indicated, and as we've heard from the panelists so far, we know that many individuals who end up being diagnosed with CTX, there are opportunities that are missed for earlier diagnosis. There are cues and symptoms that are overlooked or not factored in when different potential diagnoses are being considered. And we know that for future generations, there is the hope that newborn screening and earlier diagnosis, as everyone has said, can be implemented and that

individuals can be diagnosed and treated more easily. And we have one such experience here to be shared with Narinder Ghara. And Ghara, we're interested in hearing your very unique story this morning. Thank you for being with us.

Narinder Ghara (01:21:17):

Kim, hi Nell how are you?

Kim McCleary (01:21:23):

Great, thank you.

Neel Odedara (01:21:23):

Thank you for joining.

Narinder Ghara (01:21:23):

Thank you so much. My name is Narinder Ghara and I live in Yonkers, New York. I am the mother of five month old baby, baby boy. His name is Sarnursingh Ghara. And my son was diagnosed with the CTX when I was still pregnant. I have been told that he is the youngest person diagnosed with CTX in the United State. This has presented us with some challenge, but thanks to God and our doctors. Also some possibility allow me to share a little bit of my story. Our first son was born in 2011. Early in life, he has some kidney issue and medical issue and then he went through two surgery, 2012 and 2013. Then I was so much stressful those pregnancies also after pregnancy too. And then we're going to decide we don't need the other baby. And then 2018 and my son asked me, everybody has a sibling so why I do?

Narinder Ghara (01:22:30):

So then in 2018, I tried to, so I'm going to make an appointment with my OB. So make sure everything is okay because I'm 36 years old. So then my OB-GYN told me so later to my son, he had a kidney issue. So you have to be do the genetic tests around 2018. This my test come back as normal. Except one thing they did the 270 tests, genetic tests, everything's not normal. And one problem comes they told me is, I carried a CTX. I didn't know that. What is that means? To be honest, I didn't take like it was serious. I don't know it was that, so I never had that experience with my family or I heard the first time, this word. So in 2019, I become pregnant with the ectopic pregnancy.

Narinder Ghara (01:23:41):

I got pregnant again, 2020. Because of my CTX status, they did the amniocentesis test, 18 weeks pregnant and our baby of CTX, this how he was diagnosis. At that time, the doctor said that it was early enough to end the pregnancy, which was like, so emotional and our religions are not allowed us to kill the baby in the womb. I'm a mother womb, you know? So I decided, no, I'm going to... I asked my consult, what is that on that? You have any treatment for that? And she said, I really don't know. And she said, you can make the appointment with that pediatric genetic. So which I made it. And she said, maybe your other son should be, he's also having, we never know him because he's nine year old. Sometimes symptoms start after nine or she asked me he had a diarrhea.

Narinder Ghara (01:24:49):

I said, no, he's normal. So she said I use the [inaudible 01:24:54]. I said, he had a [inaudible 01:24:56] last three years and normal [inaudible 01:24:59] little bit weak, but he wearing the glasses, but no,

nothing, any CAT record, something like that. And I made the appointment of pediatric genetic and I consult me and my husband and my son is also because I want to be a test for him too. And is it like a stress is both side with the babies also and elder son is also because my worry is about him too and the baby is also.

Narinder Ghara (01:25:31):

So then they decided they took the blood to my son also. And then Dr. Berlin, she talked, tell me too about the CDCA treatment, which she said like after week in a start after right where baby born, we're going to start the treatment. So those time, I didn't know that that's the like CDCA medicine we have to give them three times a day to the baby. And she said this as a medicine that is the whole life. So she explain everything. And she asked me like, do you have one to keep the baby? I said, yes we want to be. We don't want to be making anything wrong with the season with them. And then, oh my God.

Kim McCleary (01:26:24):

Ghara maybe you can tell us how things have gone since your baby was born and how he's doing now.

Narinder Ghara (01:26:31):

Yeah. So when he was born, he had an MRI on day two, his brain appeared to be normal. At two months, we start him to load those treatment. All through it was very difficult to get him to use to. We tried with the bottle is also, and the orals also. But I think he realizes I'm going to give him something he don't want... He feels that bottles also. Some a week or two weeks. And he choke to two to three times because when we give it to him that medicine and he thinks something wrong and he don't want to be a swallow, but that's the liquid form. My thinking and the ball is stuck in his throat and he can swallow that. And which make me so difficult times I had it those time. Thank God after like one month, he be okay to use to, with the medicine.

Narinder Ghara (01:27:37):

And then we worked with the pharmacy and the doctors also and prayer to the God, to all the time. Now he's five months old and he is growing and reaching normal weight. He's very active. And he's starting the wallows and make sound. And he is playing with this elder son or elder brothers also. And we know we are lucky to have gotten diagnosis early and see the medicine is as a blessing. Our oldest son is tested, does not have a CTX. Even he's not carrier. He's 10 years old almost. We know that God have a plan for everything. And I'm really thankful all the genetic teams who help us as a family, whenever whatever, I haven't any question day and night, whenever I can ask email and they give it to me right away answer. So I feel like I have other families, so who are going to help me. And this is... Sorry to be emotional.

Kim McCleary (01:28:52):

Oh, it's understandable.

Narinder Ghara (01:28:54):

We hope our story give other families hope because they starting the new newborn screening. If any parents become like that's our experience and give families hope, so that's it. And thank you to the God. I think he's under the good care of them.

Kim McCleary (01:29:20):

Thank you so much, Ghara what a pioneering spirit, you and your family have to be so early in what we hope is a better pattern of getting very early diagnosis and hopefully early treatment. So thank you for all you're doing to help us better understand the care of young, young, young people like your son with CTX, and also to be with us here today. And what your story really helps us understand is this big continuum from Ghara's experience being diagnosed, her son being diagnosed still during pregnancy, all the way to someone like Debra, who doesn't get a diagnosis until almost in her forties. And so that's a lot of ground to cover. And we know that not everyone's experience starts with symptoms as Ghara has just explained. And Catherine your experience is a little bit different than the others that we've heard this morning. So glad to have you with us and happy for you to share how you came to be diagnosed with CTX.

Catherine Zonsky (01:30:28):

Well, good afternoon. My name is Catherine and I live in Flushing, Queens, New York. Thank you for allowing me to share my story today. After college, I was upset about something and with a little bit of a bad temper, I punched the back porch. That trauma led to a bump forming on the tendon of the middle finger of my right hand. My mom said it served me right for having a bad temper. The bump was unsightly. So I saw a hand surgeon and he removed the bump. Following the surgery, he told me that it was more complicated than he anticipated because the mass had grown through the fibers of my tendon. He had to slice off the top of my tendon to remove it. So I needed occupational therapy following to have full functionality of that finger. Within a few years, the bump through back. And I don't know if you can see that on the camera. At that time, my mom said it was time to find out what this is because it was not normal.

Catherine Zonsky (01:31:25):

This was in 2007. She urged me to see my father's former heart surgeon at NYU. He wouldn't be the one to fix it, but hopefully he could recommend someone. He directed me to the lipid center at NYU as a starting point. I called the lipid center and they scheduled an appointment with Dr. Edward Fisher, who I credit with saving my life. He examined me and took blood samples. After listening to my story and my symptoms he concluded that I might have pseudostell arrhythmia or a condition he had heard about at a conference called CTX. He reached out to Dr. Gerald Salen and had my blood samples sent to him. After the blood went through a special spinning process used to diagnose CTX that diagnosis was confirmed. And the bump on my hand now had a name, which is Xanthoma. I met with Dr. Salen who examined me and determined that the thickness along the back of my achilles tendon on both legs was also Xanthoma.

Catherine Zonsky (01:32:28):

That thickness runs from mid- calf down to my ankle. Those growths ache at times, if encased in boots or heavy weights like boots and skis, I was then started on a regimen of chenodeoxycholic acid taken in pill form twice daily. When my journey began, the medicine was not available in the United States. And my medication was sent from England. So later, a medication called Chenodiol became available in the United States. And that medication is sent to me monthly, by a company called Eversana. I experienced some gas and bloating, but I'm unsure if that is related to CTX. I'm also always tired or fatigued. But when I mentioned this to Dr. Salen, he did not associate that as a symptom of CTX. I had the bumps on my hands and ankles, but thankfully I have not experienced the neurological complications thanks to the fact that the medication takes the place of the enzyme that does not function properly in my body. This medication is the key to helping patients diagnosed with CTX to live full and healthy lives.

Kim McCleary (01:33:39):

Thank you so much, Catherine, a very different experience, and we're so glad that Dr. Fisher saved your life and that you've done so well in spite of the diagnosis and lucky for the treatment that has given you so much added Vim and vigor, and you bring up an interesting point about whether some of the GI distress you experienced the pain, the fatigue might be connected to CTX. So Nell, this seems like a good time maybe to go to our next polling question and see what the community tells us about their experience of those symptoms and others.

Neel Odedara (01:34:17):

Yes, absolutely. Thank you. So, we have our next polling question up on the screen now. Again, for those of you who weren't able to join for the earlier polling questions, the address to participate, if you are a member of the CTX community is pollEV.com/CTXpfdd. Our next polling question here is, before receiving treatment for CTX, what symptoms had a severe or moderate impact on you or your loved one's life? Please select all that apply. And I think just if we take a moment just to appreciate the sheer spectrum of symptoms here, I think that it is important to note just the wide constellation of different symptoms. We take that into account with the different times at which these may present. Some of the most common symptoms we hear about chronic diarrhea, GI distress, cataracts, problems with balance difficulty, swallowing, shaking, tremoring, small stature, pain, Xanthomas, difficulty with memory, depressed mood or anxiety, fatigue or problems with stamina. I will note that even just speaking from my family's personal experience, the timing in which some of these symptoms that you may first come to notice them, it really does vary. And as a result my sister is certainly, I think, experienced GI issues when she was very young. And it was only later on and issue is in her mid teens that we noticed her small stature or frailty. I think that all of this is to say is that there's very broad spectrum of symptoms. Many of which may be missed. And I think that that's something that's coming clear here in our polling results, where we see such a diverse spread across the symptoms that are the members of the community are reporting. I'm seeing 14% of participants mentioned difficulty with memory, thinking, processing information, around 10% reporting those GI issues, 8% reporting cataracts, or vision problems, 10% reporting issues with fatigue or problems with stamina.

Neel Odedara (01:36:43):

And I will note I think one of the added difficulties that may be underappreciated with even just being aware of the symptoms is when you take into account some of the memory issues, sometimes patients may not even remember, or be able to accurately recall their symptoms when they experienced them. And that just adds the difficulty and underscores the importance of caregivers, I think in this space.

Neel Odedara (01:37:09):

So we want to thank everyone for participating in this polling question. With that, I think we can move on to our next one which is, what symptoms currently present the greatest difficulties? Please select the top three. Just as a reminder, again, this is for those in the CTX community. The options here are the symptoms that we saw on the previous polling question. But I think we're already seeing a clear... Well everyone seems to, there seems to be an experience of each of these symptoms. Clearly the ones that are coming through is having the most profound impact, difficulty with memory, fatigue. We're seeing difficulty with memory around 23% and 14% reporting the top three issues being fatigue, problems with stamina. And it looks like right now as we're seeing those top three symptoms really being top three most burdensome symptoms, being the problems with balance, the difficulty with memory followed closely by the depressed mood or anxiety.

Kim McCleary (01:38:22):

That's really interesting in terms of the shift of all of the symptoms that are experienced maybe before treatment and how the things that persist and maintain as an issue for individuals even after treatment. It's just how much of an impact the memory and information processing and mood and anxiety are clearly burdensome.

Neel Odedara (01:38:48):

Great. And I do think at this time, we actually have a caller on the line. We have Tom from Raleigh who has some perspective to share on some of the symptoms that he's experienced that have been most impactful. So I just want to confirm, Tom, do we have you on the line?

Tom Johnson (01:39:09):

Yes, I'm here.

Neel Odedara (01:39:12):

Great. Thank you, Tom so much for dialing in and thank you for being the first among our callers to dial in. We appreciate you being the first to lead the pack here. We'd love to hear more about your story.

Tom Johnson (01:39:29):

Yeah. So I'm calling, I'm a caregiver and my wife, Debra, we did a video a little bit earlier in the session.

Kim McCleary (01:39:36):

I thought that was you Tom.

Tom Johnson (01:39:37):

I just wanted to reiterate, yeah. The physical symptoms, the neurologic disease, the chronic fatigue had been very challenging and affected daily life. But it's that cognitive element that at least in Debra's case has been the most challenging, which is why we just felt it was so important to participate. Because I think earlier diagnosis and earlier treatment is critical since many of these things are not reversible. And at least in our case, we found that giving the appropriate treatment can really help to put a limit on continued decline with many symptoms or some symptoms and at a minimum throw the progression for her, at least at the cognitive decline, which has been so important for us.

Neel Odedara (01:40:34):

Right, absolutely. Thank you so much, Tom. I would completely agree. I think that even speaking from my family's experience, it's certainly the difficulty of the cognitive symptoms, the wide variability, even being able to address and diagnose those I think is certainly been... It makes sense why we're hearing that those are among the greatest difficulties. So thank you so much for calling in Tom. Great, and I'll just say as a reminder to others listening in that number to dial again. We'd love to hear your perspective. That number to dial is +1 703-844-3231 that's +1 703-844-3231. Thank you.

Kim McCleary (01:41:24):

You know what this conversation is already, I think illustrating is that wide spectrum of severity of CTX from sort of a mild case. Catherine, if we take your example to someone like Eric, Sue's son we heard about from her video who remains profoundly disabled, even after treatment and Shannon, I'd like to

bring you into the conversation your son, Eric was diagnosed about three years ago. Please share with us kind of what's top of mind for you and what some of his greatest burdens and your biggest concerns are as his mom.

Shannon DeLaMar (01:41:59):

Oh, thank you, Kim and Nell. My name's Shannon DeLaMar and I'm from Champaign, Illinois. I am mother to a 19 year old named Alex who has CTX. And he was diagnosed in 2017 at the age of 16. We had sought no early medical intervention for Alex because he went from my very coordinated kindergartner that would play any ball that you threw to him, rode his bike, to losing the ability to run and jump by age 10, losing the ability to ride his bike by age 12. And this was despite years of physical therapy and many doctors. We ended up with a diagnosis of double jointed illness on the right side, because nobody could figure out what was happening. Puberty seemed to turn on some more problematic neuropsychiatric symptoms for Alex, obsessive behaviors. His high school would call me a few times a month and ask me to pick him up because he was dysregulated and needed to leave.

Shannon DeLaMar (01:43:06):

So this caused us to seek more medical testing. And by then his triglycerides were 400 despite having normal blood sugar and body size. So finally that result, plus some other irregularities in his blood, cause a pediatrician to refer us to a geneticist, thank goodness who diagnosed him with CTX. And he began treatment with Chenodiol, which I am so grateful for. The doctor ordered some tests and diagnosis to make sure, to find out where the unmetabolized cholesterol had accumulated in his body. So he had a bone scan, which at the time of diagnosis revealed he had osteoporosis, particularly in his right hip. He's brain MRI he was 16 was that of a 40 to 50 year old. He had white matter deposits. His X-rays showed development of a 40 degree curvature in his spine. So I asked the doctor, would these medical issues was all with treatment?

Shannon DeLaMar (01:44:08):

And the answer was, we don't know. Treatment did improve some of the neuropsychiatric symptoms a bit. I can report that after three years of treatment osteoporosis has increased. The good news is, is brain MRI is stable. Meaning the white matter did not increase, but the deposits that were there at diagnosis did not resolve or reduce. His X-rays are stable, but he'll have to have X-rays every two years for the rest of his life and we're considering spine surgery. Today, I'm happy to report Alex attends junior college and is pursuing acting. I want Alex to have a productive and happy life, and I'm glad he has an outlet for his anxiety. My biggest concerns are the mental health issues. He continues to experience emotional mobility, obsessive behaviors, and anxiety, even last week. He became obsessed with an issue...

PART 3 OF 7 ENDS [01:45:04]

Shannon DeLaMar (01:45:03):

Even last week, he became obsessed with an issue and it took me being very calm and asking him very targeted questions to help him realize he didn't have an issue. I worry about who's going to do that when I'm no longer living. I guess I have to trust in God. I hope this information contributes to a better understanding of CTX and how it affects lives, not just the patients but the families. And we are so happy to see CTX get this attention today. And I hope today's meeting leads to a better understanding and a healthier future for Alex and all the patients represented here today.

Kim McCleary (01:45:37):

Thank you so much, Shannon. And can only imagine the challenge of helping Alex navigate this difficult experience with CTX and how you look toward the future and all the uncertainty that both of you see ahead in terms of how to best have him have that happy and productive life that you mentioned. And it really does, I think, underscore just how even the diagnosis and the treatment isn't the end of a journey, it's kind of the beginning of a new one. And all the things that we hear or read about CTX in the medical literature just really don't seem to do justice to what all of you are bringing forward. And you mentioned the effect on yourself, Shannon, and Dr. Duell had mentioned that when he treats a CTX patient he has to treat the whole family. And Kay, I know for you with two sons with CTX, that as their caregiver you can probably relate to some of what you've heard and also help us understand what it's like to parent two children with CTX and how that affects your whole family and interactions and your family life. So please share with us your experience from Norway.

Kay Fischer (01:47:03):

Yes, absolutely. Thank you. Hello, my name is Kay and yeah, as Kim said, we live in Norway. We have two boys at the age of eight and 12, and both of them were diagnosed with CTX when they were six and 10 years old. My oldest son was diagnosed first with epilepsy when he was three years old. He is underdeveloped mentally and intellectually with poor speech and poor learning abilities. Around seven his tremors started, and when he was nine years old he was operated for cataracts on both eyes. Shortly after that surgery, he was diagnosed with child autism, or in the child autism spectrum.

Kay Fischer (01:47:54):

My youngest son, the other one, he has not been affected by CTX as much. And he's been diagnosed with toddlers diarrhea, which instantly stopped when we started to give him CDCA. Later, around six, he's been diagnosed with ADHD. He's also underdeveloped intellectually, but to a much lesser degree than his brother.

Kay Fischer (01:48:25):

They're both small and weak in statue, and everyday tasks are very challenging like personal hygiene and even leisure activities. So both of the boys have their own set of challenges and we, as parents, have to handle lots of doctor appointments and follow up meetings and meetings with specialists and other caregivers and helpers. And we manage loads of medication. And the CDCA is especially challenging, because we are making the mixture every four days and it spoils quickly and it's sensitive for a change in temperature, which is quite challenging in Norwegian climate.

Kay Fischer (01:49:16):

The situation as a whole has become very difficult for family life and us as parents. Yeah, it's very difficult for us as parents. Because my wife and I, we have become a team of nurses and psychologists and social workers. We are activators for the boys, and we had to even become specialists for lots of children with special needs, just for them to get their rights. And we have to use a lot of time and energy to do that.

Kay Fischer (01:49:50):

So you can say that life has become about managing and taking care of the boys rather than doing typical married life activities, or being a loving couple. So we both got depressed, we got depression, and that ultimately led to divorce. So we both had to seek therapist's help to be able to deal with the

situation. And my biggest problem with it is that I have to accept that the boys will probably have to have for the rest of their lives, and they might not be able to live an independent and fulfilling life. Which every parent, of course, is dreaming of when you hold your little baby in your arms. But still, we are trying our best, we're trying to teach them everyday things like showering, brushing their teeth, but we really don't know what we can expect. And we don't know what they can learn by practice and what they can learn at all. Yeah.

Kim McCleary (01:51:07):

Oh Kai, every time I hear your story you bring such a smiling face and optimism to just a heartbreaking experience for your whole family. And I can imagine you're the first of the community members who has more than one child effected. And I wonder, what is the relationship between your sons? How do they get along with one another? How do they interact? Especially since their abilities are somewhat different.

Kay Fischer (01:51:40):

Yeah. My younger son, he's very effected of my older son's behavior and his challenges. So he does not really have a normal place in the family as a young brother and the youngest son should have. It's difficult for him to understand why his brother's the way he is. And he, for example, has to deal with other kids commenting his older brother's odd behavior in school, for example. And he probably feels like he's not seen as much, at least as much as he should have been seen, and that his needs stand behind the needs of his brother. And that seems to be very unfair, and is often a source of conflict between the two.

Kim McCleary (01:52:31):

I can imagine. And Nell, you might feel some sense of recognition of those dynamics from your own family experience.

Neel Odedara (01:52:40):

Absolutely. And Kai, thank you so much for sharing that. I think that that's an experience that we can certainly relate to in our family. And my sister Sangha is the middle sister, and I think that really the challenges of navigating the differences between siblings as a result of the condition, and then especially in childhood when you don't appreciate and you can't sometimes fully appreciate why someone may be smaller, weaker, have more difficulty with things, I think really underscores the importance of understanding the wide symptomatology of CTX and the different ways it can represent. And I, again, appreciate you sharing that story with us to help us further that understanding.

Kay Fischer (01:53:34):

Sure. Thank you.

Kim McCleary (01:53:35):

I want to offer any... Shannon, maybe some of that and the dynamics of just navigating your family life might also ring true in terms of some of what Kai shared?

Shannon DeLaMar (01:53:53):

Oh, absolutely. The siblings kind of thought, "He's faking it." I finally could say, "Could he fake osteoporosis in his right hand? Can he fake his brain MRI? No." And now they understand. Just when they were younger, and especially when we didn't know why these things were happening, it was very difficult. I can relate, Kai.

Kim McCleary (01:54:17):

So profound to hear how much dismissal there is of the symptoms, of the symptom complex of even medical tests that come back with abnormalities that somehow are brushed away or not taken as seriously as they could be. I see that we have a caller ready to join the conversation. Nell?

Neel Odedara (01:54:40):

Yes. I believe we have John calling in from Portland, Oregon. I just want to remind everyone as well, if you have an opportunity to call in as a member of the CTX community, that number is 703-844-3231. We would appreciate any and all perspectives that you can share. And with that, I just want to doubly thank John from Portland for calling in. John, are you able to hear us?

John (01:55:07):

I am. Hi Nell and Kim and everybody. I'm thankful for being here. Thanks for taking my call, and good to see everybody that I've heard from and talked to before. I just wanted to touch on a little bit, some of the key questions of this facilitated discussion.

John (01:55:24):

Number one being, what are some of the challenges of getting appropriate attention in search for a diagnosis? And I think some of this was corroborated with some of the testimony we've heard today, and that is specific to what I would consider still needs to be improved, but the remaining lack of awareness in the various disciplines across the various areas of the medical community that might be CTX patient. Specifically in my case, it was the diarrhea for Ashley where pediatric GI, and listening to Kai's statement about his children and the toddler diarrhea situation, that was what we ended up getting diagnosed with, and he was sent home. And then specifically to the cataracts, I have other family stories that aren't here today to talk about their children getting cataract surgery and just being sent home with glasses and neurological disease progressing in that perspective. I'm hoping that with some of this meeting today, that we can start to... It's improving, it's getting better, but improve the awareness across the various medical disciplines so that we can lead to earlier diagnosis in while we wait for newborn screening to be in place.

John (01:56:37):

And then second, I would like to touch on Kai's situation regarding family situation, that scenario with his wife and him. I fully experienced that and, like him, I am also divorced. So this situation have has far reaching impact, not only with the effected individual but across the family. And then lastly, I also wanted to touch on the siblings experience, the unaffected siblings. And it was really not made aware to me or we were oblivious because we were so focused on Ashley's treatment and condition, that my son felt in some ways that he was sort of being second class in the family organization and expressed that to me. And like Kai, lots of therapy. I ended up being a single father of two teenage kids, one with CTX, and it was difficult. And I just want to highlight that as something that really is an extension of caring for a young individual with CTX.

Neel Odedara (01:57:42):

Yes, absolutely. Thank you. Thank you so much, John, for sharing that perspective. I think that a number of things that you mentioned here ring true, at least personally. And I recall when sister was first diagnosed you and I spoke, so even even now three years later you're still a continued source of help and of guidance. I will add on the point that you mentioned around just sort of navigating the symptoms and the dynamics within the family, one thing that I think is critically important is being able to have mental health support. I think that that's often unappreciated, and certainly something that our doctors have underscored as a continued sort of channel that you need to maintain through post-diagnosis. So thank you so much for sharing that.

Kim McCleary (01:58:42):

I'd like to take a moment just to circle back, Catherine, on your experience. And we haven't heard too much yet about the xanthomas, but you showed us your hand when you were speaking. And just wonder, what's the impact of having that on your hand? Does it affect your identity or self image? Or in addition too, you mentioned the pain in your feet, but is there pain associated with the xanthomas?

Catherine Zonsky (01:59:15):

Not the one on my hand. I mean, it is certainly is a topic of conversation. People may know me for a couple of years and all of a sudden they're like, "What happened to your hand?" I'm like, "It's been there since you met me." Little kids often say, "Is that a bug on your hand?" I'm like, "No, it's a cholesterol deposit." I mean to have it touched now... I saw someone, a doctor, recently for something else and he... Of course, right away it's a medical lesson for any doctor that you meet with. "What's CTX?" And then I have to explain everything and it's a little medical lesson for them. And he looked at my hand and he's like, "I might be able to do something with that," but I'm a little leery to it now that I only do have half a tendon, and what that might do to the functionality of my hand. My ankles do ache at times. I have some discomfort there. Again, usually if they're encased in any kind of boots or anything where it's more constricted, but overall it hasn't significantly limited me in any way.

Kim McCleary (02:00:12):

Thank you. It's good to have that additional impression and experience with that dimension of CTX as well. I'm wondering Ghara, as you're taking this all in and learning from your fellow community members about some of the issues they've faced, how are you receiving this information? What's it like to be on the forefront of a very early diagnosis that everyone keeps talking about, but also the challenges that you've already faced with both getting your son to take the medicine and getting the MRIs and all the doctor's appointments? Kai made mention of that, just it's a full-time job I imagine, just keeping up with the care.

Narinder Ghara (02:01:01):

Yeah, after heard everyone's stories I think I'm luckiest person in the room. Everybody's like front of nothing, my pain in front of everyone. Everyone has went through a lot, a lot of pain. So if I understand, [inaudible 02:01:19] a million thanks to God to help me and help him. And my wish is all the time to my son and all the community, please, God, help to everyone. All the child. And he is becoming like normal the child. Because I heard the story and make me so, so scared. Which is positive point, he's taking the CDCA. Hopefully his doctor tell me he will develop like normal baby. Which is a big relief for me.

Kim McCleary (02:01:56):

Yeah, of course. Yeah. And it's so important to have you with us today because, as we've already heard, this constant refrain of early diagnosis, early treatment and all of the heartache that that could maybe help to avoid if children were detected sooner and treated earlier. And I know-

Narinder Ghara (02:02:23):

[crosstalk 02:02:23].

Kim McCleary (02:02:23):

Go ahead, I'm sorry.

Narinder Ghara (02:02:24):

It's a little bit painful when they draw the blood every three weeks. So with a little, small baby it's like with every three tubes, after two weeks and three weeks. Which make me like little bit-

Kim McCleary (02:02:37):

Stressful.

Narinder Ghara (02:02:37):

And then other thing, I think okay, this is best for him. This is to give him relief his whole life. We try to save him, not hurt him or anything. Then with needles every three weeks, and then nothing pain to when I heard everyone's story. Everybody went through a lot, a lot of pain. Eric, usually [inaudible 02:03:09] Eric's mom, she touched with me in the messenger as well and she tells me the whole story with Eric.

Kim McCleary (02:03:20):

Another heartbreaking story.

Narinder Ghara (02:03:22):

Yeah, heartbreaking. And she said we was all place when he had diarrhea, and doctor pediatric told me maybe you give him like a extra food and fluid, and that's why he had diarrhea, because nobody knows CTX.

Kim McCleary (02:03:37):

Right. Right. Well I want to take a moment. We've heard so much already today about the potential for newborn screening and how that has been a focus of the CTX community. And with Dr. [Dubarbar's 02:03:56] advances that she's made in her lab, making that potentially possible, we wanted to provide an update on newborn screening and the efforts to get CTX included on the uniform panel. Dr. Austin Larson from Colorado Children's, couldn't be with us live today due to a scheduling conflict, but he did provide an update on efforts to get CTX included in the newborn screening programs in the US and in other countries. So if we could go now to the message from Dr. Larson, that would be great.

Austin Larson, MD (02:04:38):

My name is Dr. Austin Larson, and I'm a physician and researcher in the biochemical genetics group at Children's Hospital Colorado in Aurora. I'm pleased to provide a short update on the global efforts to facilitate newborn screening for CTX. Many of the tragic consequences of long diagnostic Odysseys and

treatment delays can be avoided. If we had a way to detect CTX in early infancy as a physician that cares for patients with newborn screening diagnoses frequently in my clinic, I have personally seen the transformative power of presymptomatic diagnosis and treatment for other inherited metabolic diseases. And I'm an enthusiastic participant in the process of adding CTX to the panel of diseases included in screening.

Austin Larson, MD (02:05:24):

Some of you may know that many groups around the world have been involved in meeting the requirements to add CTX to newborn screening panels. An application made here in the US to the advisory committee on heritable diseases in newborns and children in 2018 was discussed by the committee in November of that year, and a list of additional evidence needed was provided a month later. The committee recognized as a medically serious condition that deserves thorough consideration, and it provided a roadmap that we are now following to meet those requirements for inclusion on the recommended uniform screening panel. The testing methods that have been developed appear to be quite good at detecting CTX in blood spots used for newborn screening. There are efforts in Washington state, Oregon, New York, and in the Netherlands to test newly collected newborn blood spots to prospectively identify a newborn with CTX. We are not sure how many total baby's blood spots will be needed to be tested before the first CTX case is found, but that will be one determinant of how quickly we can resubmit the application and additional evidence to the advisory committee.

Austin Larson, MD (02:06:35):

The families participating today should know that there are many research groups committed to seeing through the re-application for inclusion on the recommended uniform screening panel. We are also preparing to have the processes in place to inform decisions about how to manage the care of newborns and young children that may be diagnosed when screening is in place. Thank you very much for the opportunity to provide an update at this important meeting.

Kim McCleary (02:07:14):

Well I hope you all are as encouraged by this news as I feel hearing it, knowing that there is progress being made and that the experience that Ghara's has had may not be the outlier some years from now as newborn screening is implemented. I know that we had another participant from the community send in a comment that kind of echoes Kai, what you were saying, and Shannon, what you mentioned about just all of the roles that you have to fill in your children's lives. Being the nurse, the doctor, the friend, the caregiver, the parent and the patient advocate all wrapped into one. And just that lingering nagging at the core of your heart, what happens when I'm not around? And Robin from Washington certainly shares that experience with all of you.

Kim McCleary (02:08:18):

I wanted to just offer an opportunity for any of you to react to Dr. Larson's update or other hopes that you have in terms of helping people navigate this journey.

Kim McCleary (02:08:42):

Catherine, it looks like you're leaning forward. Oh, sorry.

Kim McCleary (02:08:51):

Good. Well, you've said it all. You've said it all so beautifully, and we do so much appreciate you taking time out of your busy, full lives with lots of needs around you, especially Ghara and Kai with those little ones at home, and Shannon and Catherine as well. Thanks for being here and participating in today's landmark meeting. We really appreciate the benefit of your experience and expertise in helping us understand what it's like to navigate CTX. Thanks so much.

Shannon DeLaMar (02:09:30):

Thank you.

Neel Odedara (02:09:30):

Thank you everyone.

Kim McCleary (02:09:31):

Nell, before-

Kay Fischer (02:09:32):

Thank you.

Kim McCleary (02:09:33):

We'll see you all soon. Nell, before we close out and head to a break so that everyone can just relax a little bit, anything that you're observing from this conversation you want to just build on?

Neel Odedara (02:09:47):

Absolutely. I think that one of the things that strikes me as very... Is remarkable across some of the stories that we've heard today, is we've heard this recurring theme about family members trying to navigate what it means for their family member with CTX to have a normal life, to be able to achieve that. And I think that the key question, and this ties into the broad array of symptoms, is the lack of understanding around those symptoms. And I think very importantly, the differences in progression and being able to predict and anticipate what that means for how their afflicted family member may have a normal life.

Neel Odedara (02:10:33):

So I think without this sort of key understanding, it's really hard to make even basic assessments. What will activities of daily living look like two years from now? Five years from now? What does that mean in terms of the type of work that someone can take on? What does that mean in terms of what additional care or support they need in going through schooling? And I think all of this conversation just really underscores the importance of understanding, of additional research to understand the ways that CTX can represent the differences in progression, if anything the different drivers of progression. And ultimately, what that means for the different types of care, both of course pharmacological, but physical, physical therapy, mental health therapy. All of these things that can help individuals with CTX and their family members navigate day-to-day life.

Kim McCleary (02:11:29):

Oh, that's such an important point. Just the lack of predictability. And it seems almost, from the experiences that have been shared, there's this sort of infant onset form of CTX, and then maybe some

other form that comes later in life. And it really does have an impact on the trajectory and the individual's quality of life in ways we don't fully understand. And such an important direction for research.

Kim McCleary (02:12:06):

Well we are grateful to all of the speakers and participants in the community for taking part through the polling and the call-ins and the comments we've received in this first session. I know we could easily continue it for some time longer, but let's break now for a bit and give ourselves a little rest and prepare for the session that we'll come back to at 20 past the hour, where we will dedicate a panel conversation and discussion and polling questions to the treatment of CTX. We've gotten into that a little bit already, but let's explore it more fully. And then also what challenges remain, where treatment isn't maybe adequate and what the community's hopes for the future are.

Kim McCleary (02:12:52):

So with that, I'll close this session out and we'll look forward to joining you back at 20 past the hour. Thank you so much.

Neel Odedara (02:12:58):

Great. Thank you.

Neel Odedara (02:12:58):

(Silence)

PART 4 OF 7 ENDS [02:20:04]

Kim McCleary (02:36:53):

Welcome back to the Unlock CTX Patient-Focused Drug Development Meeting on cerebrotendinous xanthoma. My name is Kim McCleary and I'm moderating today's meeting along with my colleague, Neel Odedara, and we're pleased to bring you back to session two. We have another full session this afternoon and I'm going to get us started as we dive into the topic of treatment for CTX. As a reminder, any comments that are submitted in writing or by phone that we don't get to during the session will all become part of the record of the meeting and will be used to generate what we call the Voice of the Patient Report that we will be developing afterwards. The comment form is live now and you can send your comments as we're setting up this next discussion, through that and we'll see them here in the studio. You can also call in and the number is 703-844-3231.

Kim McCleary (02:37:53):

And also, on the website, you can find the meeting program, the agenda, and the discussion questions that will be focused on for this next hour and a half and a bit more. For now, we have another set of community perspectives that we'll be bringing into the conversation and then we'll go into a discussion period. Bobbi Blanchard will get us started in the set of prerecorded remarks and she's bringing in cameo appearances from her family members. And then Bobbi is followed by Robin Huard, who speaks on behalf of her son, Duane, and then Shawn Laurie will speak on behalf of her husband, James.

Bobbi Blanchard (02:38:42):

Hi, thank you so much for the invitation to share a bit about our family today. My name is Bobbi Blanchard. Hi, Jordan.

Jordan (02:38:52):

Hello.

Bobbi Blanchard (02:38:52):

My husband, Tim, and I live just outside of the Twin Cities in Wisconsin. Hi, Joelle.

Joelle (02:39:02):

Hi.

Bobbi Blanchard (02:39:02):

We have three children. Jordan is 17, Joelle is 14, and Jace.

Jace (02:39:08):

Hi.

Bobbi Blanchard (02:39:10):

Hi, Jace. Jace is eight.

Tim (02:39:15):

Come with me.

Jace (02:39:16):

...

Bobbi Blanchard (02:39:16):

Thank you. We have two children affected by CTX, and I bet you can't guess by that first impression which ones they are. That's because I say we have two of the few. We have two of the CTX patients diagnosed and treated early enough to make a significant difference in their quality of life. Seven years ago, our daughter, Joelle, had just finished first grade when she suddenly developed a hand tremor, coordination problems, and cognitive decline. Because of the neurological nature of her symptoms, her medical care team knew that there was something really wrong and they worked diligently for a diagnosis. Still, it would take a year and a half of progressively invasive testing, three different facilities, and six different specialists to finally get a CTX diagnosis via whole exome sequencing. During that year and a half, Joelle experienced rapid deterioration in her cognitive ability. She developed short-term memory problems, peripheral neuropathy, and increased problems with coordination, gait, and increasing tremor.

Bobbi Blanchard (02:40:33):

Even on our comparatively short diagnostic odyssey, our family suffered significant emotional and financial trauma. The helplessness of watching your daughter deteriorate and your medical debt rapidly increase is something we're still recovering from today. Also, with Joelle's diagnosis came Jordan's. Upon

receiving the phone call about Joelle's test results, we knew immediately that Jordan had CTX too, though he has had a totally different presentation with more typical onset. We would find out that Jace wasn't even a carrier. It took three months to start treatment with the vast majority of that time spent convincing the insurance company to approve an off-label expensive medication. Upon starting the treatment though, we noticed an improvement in Joelle's tremor and coordination fairly quickly, but she is left with many of the other problems she had at the time of diagnosis. Joelle and Jordan have had a very little progression in the last five years.

Bobbi Blanchard (02:41:42):

However, we're not without some challenges. Because of Joelle's slowed cognitive processing and her short-term memory problems, and the public school's inability to meet her educational needs, we've decided to teach her at home. Though, Jordan, now a senior in high school, has not been affected cognitively. He needs additional support with ticks, OCD, and significant anxiety disorder, which all contributed to suicidal thoughts requiring medication and continuing therapy. Both kids have needed several eye surgeries to deal with cataracts and additional buildup on the replacement lenses which has left them with continually changing vision. It seems we're always dealing with insurance on approval for something and we have considerable fears about how the kids will handle these things in adulthood without us. Another significant concern for us is how they'll handle daily medical needs. Will they continue therapies and treatment as prescribed without their parents nagging them?

Bobbi Blanchard (02:42:50):

And if they stopped therapies and treatments, how quickly will they decline and will they even know that they need to get back on track by then? What happens if insurance decides that they won't cover their medication? If we weren't around, would they and their treatment needs just get lost in the system? We know we've been incredibly blessed to have received a diagnosis and treatment in time to make a difference in Jordan and Joelle's lives. What we deal with on a daily basis is manageable and has given us the opportunity to advocate for the undiagnosed and the diagnosed too late. So, we very much appreciate your time and this opportunity to share a little bit about our experience with CTX and being an affected family. Thank you.

Robin Huard (02:43:47):

Hi, I'm Robin Huard. My son, Duane, has CTX. I'm going to share just a fraction of what he has experienced over his 36 years with respect to the treatments he's received on his way to getting diagnosed with CTX at age 31. And since then, our family journey with CTX has been full of many obstacles and challenges. But Chenodal has given Duane new life and us hope for his future and living with CTX. Like other stories that have been shared today, Duane's health issues began very early in life. Duane was born a blue baby and as a newborn, had plugged eye ducts which requires surgery. As an infant, he was diagnosed with asthma and he also struggled with croup and pneumonia, chronic diarrhea, and unusual tremor in his hands. Little did we know that these last two issues are hallmarks of CTX and were our first clues that something more serious was affecting Duane. During his early years and youth, Duane exhibited some signs of developmental delay and unusual body movement.

Robin Huard (02:44:47):

For instance, Duane's arms did not swing when he walked but hung at his sides. He struggled with some areas in school, especially in mathematics, but he persisted with the studies and earned his Associates of Arts at the local community college. Duane, if anything, is resilient, which has been key to him not

wholly, being wholly defeated by CTX. Like others we've heard from today, Duane was diagnosed with cataracts at age 15 which required surgery. Unfortunately, no follow-up or genetic testing was suggested by either his optometrist or ophthalmologist. And like Duane's persistent diarrhea and shaking limbs, this health issue was forgotten. In 2010, when Duane was 23, he fell at work and shattered his kneecap which required surgery to repair it. The orthopedic doctor noticed what he thought was a tumor on the bottom of his foot, later determined to be a desmoid tumor. This was only partially removed because the surgeon wanted to leave enough padding on Duane's foot so that he could walk.

Robin Huard (02:45:50):

The doctor remarked at what a high tolerance for pain Duane must have given where the tumor was on his foot and his lack of awareness of it. Duane never felt any pain. He was in two serious car accidents and walked away from both seemingly unhurt. Around this time, Duane began showing other signs of CTX and altered gait and enlarged Achilles tendons which, combined with the tumor, have greatly impacted his mobility. A few years later in 2013, Duane had a choking incidence with a piece of steak which sent us to the emergency room. A second serious incidence prompted an endoscopy exam and what eventually led to a diagnosis of eosinic esophagitis and Barrett's esophagus. Duane's difficulties in eating were the tipping point in a rapid progression of CTX and onset of a host of CTX-related and other medical issues. In the span of a few years, especially from 2016 through 2018, Duane underwent a shocking transformation, which resulted in his gradual loss of autonomy and is having to move back home.

Robin Huard (02:46:55):

He struggled to eat and swallow and meal times began to last hours. Even the consumption of a bowl of oatmeal could take an hour. Duane's weight plummeted to 102 pounds when he was most sick. To put this into context, Duane is near six-foot tall. This frightening weight loss coincides with Duane becoming physically weaker and new struggles with mobility. He began to lose his balance quite often and started falling more frequently while shopping during the holiday season. His brother witnessed him just tip over and fall on the ground. There were other health issues. The whites of Duane's eyes become yellow and a complete panel of blood tests which resulted in a diagnosis of Gardner's disease. He also had kidney stones that he did not feel to the amazement of his doctors and family. He also showed signs of cognitive decline. He was not remembering information well and conversation with him could be repetitive.

Robin Huard (02:47:51):

It was also becoming difficult to communicate with Duane because his speech was changing. His speech was rapid but muffled and unclear and his tongue quivered. He showed some signs of obsessive compulsive behavior and increasing anxiety. Duane was not sleeping well. In 2013, he was diagnosed with severe sleep apnea and periodic limb movement that caused his limbs to spasm. It took until 2019 for Duane's sleep apnea to finally be under control using an adaptive servo-ventilation machine. By 2018, Duane could no longer work and had to relinquish his job. He became weak and wheelchair-bound. He would sit slumped over and mouth ajar and drooling, speaking very little. He looked like a zombie. He was so ill. We were frightened for him and thought he was dying. We felt helpless and we're running out of hope. But as a family, we persevered, and with the help of a small army of health care providers and specialists, Duane was finally diagnosed with CTX which was later confirmed by genetic testing.

Robin Huard (02:48:57):

We finally had a name to pin his health catastrophe down to and it came as a huge relief. Duane was soon after given his first dose of Chenodal and to the disbelief of his doctors, we could see very subtle changes in Duane within the first two weeks of the Chenodal treatment. Within six months of his treatment, his quality of life improved. He began slowly walking and moving his arms and he could speak somewhat better again. The persistent diarrhea and limb tremor went away. Duane began to gain weight, eventually reaching his current weight of 163 pounds. He can absorb nutrients now. The Chenodal awakened Duane's body. And while it gave us new hope, it brought new challenges as well. The new sensations Duane was feeling, including pain, completely overwhelmed him and crippled his progress. His anxiety and obsessive compulsive behaviors went into overdrive and began to take over his and our lives.

Robin Huard (02:49:55):

Duane constantly felt like he was choking and getting him to eat was even more difficult than before the Chenodal. He resisted moving and performing the simplest of tasks, turning his head to look when people and talking to them brought on too many sensations that scared him. It took well over a year for doctors to find the right balance of medications to enable Duane to conquer his anxiety and compulsions. Duane still has a number of health-related issues that may or may not be connected to CTX. He currently takes eight medications daily. He struggles with mobility and has seen physical therapists to address this. Recently, he's began losing balance and is falling again. He still struggles while eating and chokes when swallowing and still struggles with his speech, which he is seeing a speech therapist for as well. The cognitive decline that Duane has experienced is still at present.

Robin Huard (02:50:50):

He has recently developed a lump in the right side of his neck that is currently being investigated. Duane's life is not easy. As a family, we have had to completely adjust our entire lives to take care of him. We are extremely thankful for his neurologist, Dr. [inaudible 02:51:07] and the dozens of doctors and healthcare professionals that have helped us and to continue to help us with his care. We are thankful to have determined the underlying cause of many of these problems, CTX, and to have Chenodal as the main defense to help combat it. Chenodal has truly given us hope for Duane's future and has saved his life and quality of life. Thank you.

Shawn Laurie (02:51:35):

My name is Shawn Laurie. My husband, James, and I live in Mansfield, Texas where we raised our two children. James and I met the first time in high school, then again in college, and started dating when we were 18 years old. A year later, I noticed that this athletic guy was suddenly having trouble with his balance. He could no longer bicycle or rollerskate. He developed enlargements on his Achilles tendons but he didn't pursue it because he didn't have medical insurance. He developed tendonitis a couple of years later and severe depression a few years after that. His therapist encouraged him to get his tendons looked at. That led to a misdiagnosis of MS in 1994 and treatment with IV steroids. After that, he did see an orthopedist who did an MRI on his tendons. That led to more referrals and ultimately the correct diagnosis of CTX at 31 years old. The process of getting a diagnosis for James took four years, seven doctors, and multiple therapists, and tests.

Shawn Laurie (02:52:44):

James has been on Chenodal for 23 years, actually on and off, due to challenge getting the medication at different points in time. We first had to obtain the medicine from Germany, and then from London, and it would often get stuck in customs. When James started on Chenodal, he had severe problems with walking, major trouble with his memory, and his eyes appeared dull. In the first year, we saw improvements in James's gait, his mental acuity, and his affect improved as well. When he had to go without as medication because of access issues, he would regress. And even once he was back on the medicine, he never got back to the level he was at before. James was able to continue working until 2006. At that time, he was working as a contractor and fell down the stairs at work and broke his arm.

Shawn Laurie (02:53:39):

He was laid off soon after. When James stopped working, I became the sole provider for the family. At that time, access and the cost of the medicine was our biggest concern. My job provides health insurance, and so far, our insured has covered medication, but we live with a fear that the coverage might end because it's not FDA approved for CTX. I also worry what would happen if I lose my job. CTX has robbed a lot from James and from our whole family. Today, James still struggles with mobility. He's fallen many times over the years and one of my biggest worries is that he will fall and injure himself when I'm not at home. One time, our 16-year-old son had to get him to the ER after a fall while I was at work. Our son later became a paramedic firefighter, and I think his father's condition had a lot to do with that career choice.

Shawn Laurie (02:54:36):

Here's some of the equipment that James uses on a daily basis. We have the van, a lift for the electric scooter that he uses for long distances, a lightweight walker for traveling, and this is something that I can lift easily, and then a heavier weight walker that he uses around the house. James recently stopped using a cane because he had some falls. And he in all [inaudible 02:55:04]-

PART 5 OF 7 ENDS [02:55:04]

Shawn Laurie (02:55:03):

... because he had some falls, any, and all trips are planned around accessibility. He spent many hours working with the physical therapist to improve his mobility, but physical therapy can only do so much. He has used a Baclofen pump to help with spasticity in the past. James developed thyroid cancer three years ago, which was diagnosed after he experienced problems swallowing. His thyroid was removed and he initially lost a lot of weight due to his inability to swallow and some of his mobility because he was so weak. James had a CP myotomy two years ago, which has helped some, but he still has trouble swallowing.

Shawn Laurie (02:55:39):

I fear the cancer's coming back based on the results of recent blood tests. While chenodiol has been essential to halting the progression of CTX, it didn't restore everything that was lost by the time James got diagnosed. It couldn't reverse the damage in his nervous system.

Shawn Laurie (02:55:55):

James's mood is up and down and he takes antidepressants to help regulate it. He has neuropathy in his extremities. There have been times when he told me he did not want to live any longer due to his physical decline.

Shawn Laurie (02:56:09):

More recently, James has had such a hard time swallowing the pills that we've had to try alternatives for dosing, like crushing the pills and taking them once a day instead of four times a day, which we know isn't ideal.

Shawn Laurie (02:56:22):

At age 55, we may have reached the limits of what chenodiol can do for James. I wish there were treatments that could lead to improvements in his quality of life, especially his mobility, his mood, his ability to eat, to work and to play without so many limitations.

Shawn Laurie (02:56:38):

I wonder about the possibility of gene editing or gene therapy to fix the problem in the liver rather than just treat it. I also wonder if there are possible treatment options using stem cells or LDL for apheresis. Both our children carry one recessive copy of the gene that causes CTX. Our two grandchildren haven't been tested. I hope that in our lifetime and theirs, we will see the advances of research on CTX, newborn screening, and better treatments that restore function and allow a better quality of life. Thank you for this opportunity to share our family's experience and hopes with you today.

Kim McCleary (02:57:25):

Wow. Another really compelling set of testimonies that underscore the importance of the mainstay therapy, chenodiol or CDCA in slowing or stopping the progression of CTX and relieving some of the symptoms.

Kim McCleary (02:57:41):

And we also heard about other treatments that are used to improve function and relieve some of the other symptoms of CTX, as well as treatments that are encountered on the way to getting an appropriate diagnosis that may or may not provide any benefit to the individual and perhaps put them at harm. Robyn and Shawn and Tom earlier in the session spoke to those. And we heard about access challenges and unmet needs. And we're going to come back to those. We know that this panel has a lot to say about those topics.

Kim McCleary (02:58:18):

We also want to invite more participants from the community to weigh in with their experience and perspectives through the written comments that you can see on the bottom of the webpage, where you viewing today's meeting as well as by dialing in at 7 0 3 8 4 4 3 2 3 1. And we'll also have a couple of polling questions in just a few minutes.

Kim McCleary (02:58:43):

Before we go to that, I want to invite one of our panel here to participate in the conversation. We'll hear first from George Bryce. And George, your diagnosis came around the same age as what we just heard from Shawn about her husband, James in your thirties. And so you and he have both been treated for your CTX for some 20 years now. And we just want to hear from you about how you're doing today and how you're managing your life and symptoms with CTX. George.

George Bryce (02:59:21):

Well, thank you. My name is George Bryce. I was diagnosed. Yeah, I was at my early thirties because I was having a problem running around the basis. I couldn't run around basis anymore. I went to the doctor to find out what was wrong with me. He didn't know. And so he sent me to a neurologist who didn't know after checking what if an MRI. So he sent me to the Mayo Clinic in North Scottsdale, Arizona. And he's the one that identified that I had CTX .

George Bryce (03:00:05):

They did notice I had clonus make them figure out where that happened or what that stem from, which I believe is all part of it. I also have hyper spasticity, which is something that comes from that as well as I got real balance issues. And so I've been using a cane for a while because I had... In fact just a couple of days ago. Yeah, just a couple of days ago. I was just standing there and fell over. But I've been on the chenodiol since I was diagnosed. I don't see it really getting... I feel like I've kind of stabilized and I don't know how much of the changes with balance, et cetera, that has occurred if it's because my age or if it's just a natural progression of the condition of CTX, having CTX. But I was diagnosed, it affects my spinal cord and my nervous system. I do have a couple of xanthomas [inaudible 03:01:19]. And that's how Dr. Bosch determined that I had some CTX. But so far so good. I feel healthy for the most part. I don't have any other disabilities per se that I'm aware of. But those that I do take the chenodiol for that. I take the Baclofen for the a hyper spasticity, my legs like to jump a lot, especially at night. And then I also take a citalopram for anxiety. So I guess that from what I've been listening to, it sounds like that could be part of the swell as well, so.

Kim McCleary (03:02:16):

Well, thank you, George. We appreciate your long-term perspective on living with CTX. And I think at 53, you're still a very young man. So don't chalk it up to old age quite yet. You're too young for that.

George Bryce (03:02:30):

Yeah, I agree.

Kim McCleary (03:02:35):

We want to understand you and your experience somewhat similar to James in terms of the medications that you're using in addition to the chenodiol and let's turn it over to Nell and some polling to get the community perspective on what medications are being used.

Neel Odedara (03:02:51):

Yes, absolutely. Thank you, Kim. And just to reiterate, once again. In addition to the polling, we have a number that you can dial in to provide any additional comments, share your experience. That number is 7 0 3 8 4 4 3 2 3 1. And with that, our next poll here for members of the CTX community is which of these medical treatments views to manage your CTX. You may select any of the options that apply. The options, being chenodiol, all muscle relaxing, anti- depressant medications, anti-anxiety medications, other medications, ophthalmic surgery for cataracts, or other vision problems, and then surgery to remove or reduce xanthomas.

Neel Odedara (03:03:42):

It looks like we're already getting a number of responses here. Most commonly and unsurprisingly many on a CDCA or chenodiol but also seeing that quite a few patients taking anti-depressant medications, anti-anxiety medications. So in addition to having ophthalmic surgery and other forms of surgery, so

we're seeing about a third of participants on chenodiol. But at least around 30% on some form of anti-depressant or anti-anxiety medications, and a further 20% having some form of surgery, either ophthalmic or surgeries to reduce xanthomas.

Kim McCleary (03:04:30):

I think it's important in these select all that apply questions that these bars, as we watch them sort of grow and shrink are more relative. So I would imagine it's more than 25% of community members that are being treated with chenodiol but 25% of people have chosen that but again, being more relative than absolute in this setting of the select all that apply questions.

Neel Odedara (03:05:01):

Yes, absolutely. Great. Great. All right. Well, and then with that, I think we can move on to our next polling question. So our next question here is what barriers to accessing CTX related medical care or treatments have you encountered please select all that apply. Our options being, finding a knowledgeable healthcare professional, providers that I want to see don't take my insurance or out of network, providers I want to see have a long waiting line for patients coverage or payment for prescribed medications, supply issues, coverage for supportive therapy, including speech therapy, counseling mobility equipment, and then finally out-of-pocket costs.

Neel Odedara (03:05:44):

So just as we wait for some of the additional responses to come in, I think that we can already remark that. A key challenge is finding a knowledgeable healthcare professional. I will also add just from personal experience, I think one of the added challenges, if you're being seen in an academic medical institution, just the turnover of potential providers that you may have.

Neel Odedara (03:06:12):

I know that's been a challenge for my family personally, and then having to sort of go through that process of bringing your new physician up to speed is sometimes every one and a half years, two years. I think that's certainly an added challenge to access related care, but it seems like as we see the responses coming in, solid component of members of the community saying finding a knowledgeable healthcare professional is a challenge, getting coverage for prescribed medications, getting coverage for supportive therapies, all key challenges, as well as providers that they do want to see having long wait lines and out of pocket costs.

Kim McCleary (03:07:00):

Yeah, so much emblematic of the experiences that have been shared through the prerecorded messages and our panel discussions. All of that, just being born out by the data here, the just great challenges that everyone faces. And we heard Sean spoke to it in terms of James' condition and others have brought up some of the lapses in the medication and how that can lead to regression, and then not being able to recover back to even the earlier state before you might've had a break in getting access to CDCA.

Kim McCleary (03:07:47):

I know that we have a member of the community Avril Diamond, who is the daughter of a woman, Ann living in England who has CTX. And unfortunately, Avril's mom, Ann fell last night and broke her femur. And Avril's not able to be with us. But their experience is so important that we wanted to make sure it

was part of today's discussion. And Nell's going to go ahead and share Avril story with you so that it can be part of today's meeting.

Neel Odedara (03:08:23):

Thank you, Kim. And we do want to thank Avril for sharing her experience and wishing the best to her and her mother as they navigate the recovery from the fall.

Neel Odedara (03:08:34):

I'm just going to read a statement from Avril. My name is Avril Diamond. I live in the Northeast of England. I'm the daughter of Ann Diamond. She's perhaps the oldest surviving person affected today as she turned 76 this year. My mother and her younger sister, Julian were diagnosed with CTX about 30 years ago. Her mother was in her forties and her aunt was in her late thirties.

Neel Odedara (03:09:05):

Her father passed away when she was 17 years old, and Avril has been the primary carer for her mother. Although her aunt, Julian's symptoms were more severe, they both had premier short cataracts, diarrhea, and some social and educational disabilities. Julian, or Julie had seizures and falls, had other difficulties, but it was the classic xanthomas on the Julie's Achilles tendon that led doctors to look at both and identified... Started thinking about leukodystrophy and ultimately diagnose them both with CTX.

Neel Odedara (03:09:45):

Her mother had a long history of zigzag walking, migraines, and other symptoms, and upon inspection heartening on the Achilles heel, but it was not the classic outwardly protruding xanthomas that Julie had. With the diagnosis, they were both on CDCA. But the UK National Health Service provided CDCA for many years. However, the treatment was mistakenly switched to UC or UDCA around the time the ULF [inaudible 03:10:14] began to control things in the US and there was a disruption in their supply.

Neel Odedara (03:10:19):

Avril was a child but when she realized the substitution for a similar gallbladder drug could be wrong, she began questioning and was rebuffed. But ultimately fought via NICE to bring the drug to the UK and provide the right treatment at the time that her mom had become the sole surviving diagnosed case in the UK, that she was aware of in the cost of the drug had spiraled.

Neel Odedara (03:10:45):

She emailed a CT expert, Dr. Gerry Salen, who we've heard from other members have interacted with to reach out for his advice on whether UDCA was an acceptable substitute in the treatment of CTX, instead of CDCA. And Dr. Salen responded to Avril unequivocally that UDCA was an ineffective treatment and only CDCA would mediate the CTX. Had he not been alive at the time she's not sure that she could have approached him and she's forever grateful that he replied.

Neel Odedara (03:11:22):

She used his email and in repeated appeals with NICE and medical professionals and pharmacies in the UK. She estimates that the fight went on at least 18 months from realizing the medication had been changed and in that time, Julie may have been on UDCA from earlier than her mother or even longer.

Her aunt Julian, and her mother, both began to decline. Julie lost her ability to talk, walk developed a swollen third world malnourished like belly problems, swallowing and drooling, feeding via peg tube, she went on having increased seizures and falls to being in a wheelchair full-time. No longer able to bear weight nor stand nor able to hold herself upright without trunk support. Her aunt Julie developed gallbladder problems, sepsis, and sadly passed away at the age of 59 before she was able to get her back on CDCA treatment. Avril's mother regressed as well, but fortunately, Gerry's email meant that she could get her back on the medication in time to save her. Avril's mother is now 76 years old. In addition to CDCA, she's trying to learn from and use nutritional support, digestive enzymes, and physiotherapy approaches like Pilates and leg and core training to help her retain as much function and as much quality of life as is possible for as long as possible. They live by the statement, use it or lose it. It has been hard to continue the physiotherapy during COVID and finding private therapists willing to work with her mother. But they're doing the best and they can't meet the new challenges as it comes and there are many new challenges.

Neel Odedara (03:13:18):

Avril will become her mum's 24/7 care when she needs me, I am very proud of her but if she doesn't continue to use it she will lose it. So I've got to enable her to do the simple things every day we take for granted for herself, as long as she can. Avril mentions that there's lots to learn. She's learning, and they're learning this ourselves. There's a lot more that can be done for CTX patients to maintain strength and gut health and vitality. And more is needed to address the damage to the brain, which couldn't happen earlier and more to contain the condition.

Neel Odedara (03:14:03):

Patients and caregivers have valuable insights. Everyone is different, and there's not one treatment for all and all individuals, more help is needed per the degree of gene fault. Avril wants to thank us for keeping our minds open to the treatments as yet undiscovered and beneficial to our loved ones in an evermore advancing world.

Neel Odedara (03:14:25):

She wants to thank us for the opportunity to share her experiences. And she hopes that this information contributes to a better understanding of CTX and how it affects the lives, not just of patients, but the entire family. And we do want to thank Avril again for sharing this powerful statement and for sharing her experience.

Kim McCleary (03:14:44):

Thank you, Nell. And it's a shame that Avril couldn't be here to share that with us herself. Their story certainly underscores what we heard from a number of community members, not only today, but as we were preparing for today's meeting, just the intense fear that families feel about the potential to lose access to the mainstay therapy, chenodiol, and what that might have or lead to as consequences for that lapse in treatment. Anything you want to just build on?

Neel Odedara (03:15:20):

No, I would add, I mean, even personally, I have the experience of having a minor panic attack whenever I get a call from our sisters in insurance company mentioning the sheer uncertainty around the continuing coverage. So I think that that's something that's likely echoed across the community. And I think that that's a very important additional burden on families to highlight.

Kim McCleary (03:15:47):

I see Bobby is with us on the phone and wants to share, build on what she had indicated in her prerecorded statement about the access issues. Bobby, are you able to hear us and take part in the conversation?

Bobbi Blanchard (03:16:05):

I am.

Kim McCleary (03:16:06):

Welcome. Thanks for being here live-

Bobbi Blanchard (03:16:09):

Thank you.

Kim McCleary (03:16:10):

... and by your beautifully produced video.

Bobbi Blanchard (03:16:15):

Thank you. Thanks for the opportunity. I think just speaking to the fear of access to medication, there is fear of them not having the specialists and the insurance that they need to get the kind of therapies that they need. Right now, both of our kids are on Tim's insurance, which has been incredibly grateful for both because just through the diagnostic journey, we were able to see a lot of specialists that we wouldn't have been able to see otherwise, even though there were significantly [inaudible 03:16:48]. They did accept his insurance. Now, it's just like what happened now with COVID where Tim was laid off, then there was concern over can they continue to see the specialists that they need to see, and what happens now? At some point when they are off Tim's insurance chances are with some of the difficulties that they have they won't have the kind of jobs that is going to provide the kind of insurance that they need in order to see some of the specialists that they've needed. So just not only access to medication, but access to the specialist [crosstalk 03:17:32] something.

Kim McCleary (03:17:33):

Absolutely. Thank you, Bobby, for adding and building on the comments of others. We really appreciate having a better understanding of all the ways in which access can be constrained and perhaps imperiled for your family.

Kim McCleary (03:17:52):

I know there are other circumstances where physicians may not have information or understanding about the treatment. And one of those is when women with CTX become pregnant. And Holly, you had an experience when you became pregnant, having been diagnosed and treated and just the uncertainty around that period of your life, please share it with us.

Holly Rosengrant (03:18:18):

Sure. My name is Hollisa Rosengrant, and I live in Chicago, Illinois. I was diagnosed with CTX 13 years ago at the age of 27 after I had surgery to remove a suspicious growth on one of my tendons IN my finger. I was very lucky to have an orthopedic surgeon and his team who did thorough research that led them to

believe I had CTX. I was then referred to doctors in Oregon, which Dr. Duell, who spoke earlier this meeting and he is my current treating doctor. So I went to Oregon in 2008, stayed there for tests. I was officially diagnosed with CTX and I started my treatment with chenodiol.

Holly Rosengrant (03:19:03):

I was fortunate that the xanthoma at the time was the only CTX symptom that I had. I did have cataract stack when I was in high school. And that was in the late nineties. And wasn't very well known about CTX so it wasn't anything. It was just unfortunate luck is what I was told to have cataracts this young.

Holly Rosengrant (03:19:32):

So now that I'm 40, I do have some gait issues when I walk [inaudible 03:19:38] I haven't fallen and hurt myself, but it is a paranoia I live with, so yes. But one of the biggest challenges I've had living with CTX is when I became pregnant four years ago with my daughter. There wasn't much evidence to go on whether chenodiol was safe to take while pregnant. So I was referred to a maternal and fetal medicine specialist who right away told me stop treatment, do not take it. But what he was seeing was when chenodiol was being used to treat gallstone, it was black box. It was unsafe to take when pregnant.

Holly Rosengrant (03:20:23):

I did talk to Dr. Salen, Dr. Duell, and they both agreed treatment was safe because they've had other patients who were pregnant as well to continue. So I asked my medicine specialists to please talk to my other doctors and see if they could change her mind basically. And he did agree after the phone calls that I did need to continue my treatment.

Holly Rosengrant (03:20:51):

It was an added anxiety to pregnancy. The uncertainty of the medicine, the unfamiliar of the actual disease. And it was added anxiety to an already high risk pregnancy.

Holly Rosengrant (03:21:07):

When my daughter was born, the delivery nurse told me she couldn't give me my treatment because the hospital pharmacy again, so I was seeing warning labels as the specialist saw too, that it was unsafe to take while pregnant or nursing. So I feared this would happen. So I ended up just packing my own supply of medicine in my overnight bag and I continued my treatment.

Kim McCleary (03:21:31):

Piracy.

Holly Rosengrant (03:21:32):

Yeah. I mean, I knew you got to do what you got to do. So I had my daughter tested last year. She was about two and a half to see if she had CTX. She didn't have any obvious signs of it, but I'm beyond grateful she does not have the disease.

Holly Rosengrant (03:21:52):

And I hope my story and this entire meeting brings more awareness to the need of more research and better ways to address the challenges that people face living with CTX. It's a scary thing to live with, so.

Kim McCleary (03:22:13):

Oh, well, thank you, Holly. Thank you for sharing, not possibly a unique experience, but one that we had not heard before you shared it with us. So we're really grateful to have that perspective of a young mom and trying to navigate life as a new mother and a pregnant woman in the setting of so much uncertainty about the treatment and your future.

Kim McCleary (03:22:44):

So thank you for sharing that. And we've heard from other people, as we prepared for this meeting, just about some of the issues that come up with pregnancy when people are in sort of that diagnostic Odyssey, and may be on medications for other perceived diagnoses that maybe force them to put off having a family or concerns about passing on CTX to another generation and that all of those worries are very much present in the community.

Kim McCleary (03:23:18):

I want to shift gears a little bit through the discussion. We've heard about some members of the community. We heard about actually John's daughter, Ashley participated in some of the early trials of CDCA to demonstrate its effectiveness in treating CTX. And there are other potential experiences with experimental therapies. And we have with us, Estefania Amyerich from Spain whose two sisters have CTX. And one of whom has had an experience with an experimental therapy. So Estefania thank you for joining us in your evening time and being part of this meeting today.

Estefania Amyerich (03:23:56):

Thank you. Thank you. Okay. My name is Estefania Amyerich and I live in Vigo in Spain. I have two sisters with CTX. Lurex is now age 48. She was diagnosed at age 25. Noria is currently age 41 and was diagnosed at age 18. Both are treated with [inaudible 03:24:24]. My oldest sister is more severely affected, especially in terms of her neurologic function. She has continued to deteriorate in spite of more than 20 years of treatment. From being a happy and proud young woman now she cannot carry out an independent life.

Estefania Amyerich (03:24:44):

One of the most despairing effects of CTX for them and for our whole family is that both have experienced suicidal thoughts and attempts. This seems to be a serious [emerging 03:24:58] problem that we hear a lot about here in our CTX community in Spain.

Estefania Amyerich (03:25:04):

The severity of my older sister's conditions caused us to look into more experimental treatments. Based on my report policy in 1993 in Japan, our doctor worked to get her treated with plasmapheresis under the possibility that it could remove the toxins from her blood. The treatment was very expensive. It was not covered by our public health system and it was not available locally so we had to travel frequently and spend long hours in the reference center.

Estefania Amyerich (03:25:37):

In spite of some sign of neurological improvement, the benefit did not justify the cost and hardship of the treatment. And we had to discontinue plasmapheresis after 12 sessions. I operate a smaller organization to connect people living with CTX in Spain with about 20 families. Like my sisters, I hear

from the community that they need more treatments, especially ones to address the root cause of CTX like gene therapy that is our hope. We also need more treatments that are effective in taming the neurological problems, psychiatric symptoms.

Estefania Amyerich (03:26:19):

I hope that this meeting will lead to more progress and thank you for your interest in our family's experience and the needs of [inaudible 03:26:27] healing Spain. Thank you.

Kim McCleary (03:26:31):

Thank you so much Estefania. really beautifully said, in terms of the hopes, the experience of your sisters and also the hopes for the future and maybe some more primary therapies that really get to the root of what causes CTX.

Kim McCleary (03:26:47):

And that just brings up the issue you raised about the potential for gene therapies and Shawn in her prerecorded statement mentioned the hope for gene editing or other types of therapies that might be more curative. And certainly with all the advances that we're seeing in science, particularly with rare genetic diseases, I'm sure that the community looks forward to when that type of research will be conducted on CTX as well. [inaudible 03:27:23].

Neel Odedara (03:27:24):

And I think just on that, we do have some comments that are coming in from members of the community who have been listening in. We appreciate you participating, sharing your thoughts and experiences. For those of you still listening I just want to share that you can continue to provide comments over the website and I will share the number again as well for you to dial in if you'd like. And that number is 7 0 3 8 4 4 3 2 3 1. So we've had some comments from members of the community regarding treatment. So Joe, from Alabama mentions that I am a CTX patient. I don't feel like the medication is working at times. I have been getting a lot worse over time.

Neel Odedara (03:28:16):

Shannon from Illinois mentions my 19 year old with CTX has been seeing a chiropractor on and off since he was 10 years old to deal with the pain. After diagnosis he continues to see a chiropractor once a week. He has x-rays every two years to make sure the 40 degree curve has not increased. The spine surgery is being considered.

Neel Odedara (03:28:41):

And then we have Mary Beth and Mario from Port Orchard, Washington caregivers there's two adult children. We have little knowledge of what to expect for their future and how to plan for it after they're gone.

Kim McCleary (03:29:03):

Such important perspectives. And so many themes coming through today's discussion, this session and the earlier one. And kind of raises the hopes and expectations for the community that go beyond the available therapies and to perhaps what the unmet needs are.

Kim McCleary (03:29:25):

We've heard a lot about improvement for the mobility issues and sort of the progression of those mobility issues as people age and certainly for the mental health concerns and the mood disturbance and the cognitive issues that so many people experience.

Kim McCleary (03:29:46):

This setting of a PFDD meeting is a time to sort of reflect from the community on what are the highest priorities for addressing unmet needs. Kind of going across a number of different dimensions that are raised by the conversation today. And-

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Kim McCleary (03:30:02):

... mentions that are raised by the conversation today and to lead off this discussion about priorities for the unmet needs, we've invited Dr. Bob Steiner, who is a Physician and a volunteer, and one of the founding members of the CTX Alliance to share his perspective from those dual aspects of seeing patients in clinic and also being a member of the community who's invested in the future for change, for people affected by CTX. So, Bob, if you would, please share your perspective on community priorities for unmet needs.

Bob Steiner, MD (03:30:37):

Well, thank you, Kim and Nell. My name is Bob Steiner. I am a Physician and Professor at the University of Wisconsin. I encountered my first CTX patient in about 1997. Since then, I've had the opportunity to work with approximately five CTX patients directly, and many patients indirectly as both patients that doctors reach out for advice. I'm contacted for advice on CTX treatment since I've been involved with CTX research for more than 20 years, written articles and chapters on CTX, participated in continuing medical education programs on the condition, as well. As Kim alluded to, I also volunteer with the CTX community and I'm currently serving on the board of the newly forming CTX Alliance. Despite better means of detecting and treating CTX that have been developed since I started seeing CTX patients, many unmet medical needs remain. I have the following observations, which are really not novel.

Bob Steiner, MD (03:31:38):

You've heard about actually all of these today, but I wanted to bring them all together and expand a little bit. So first, treatment can't reverse all complications already present. We can't yet cure autism and CTX patients or completely resolved balance problems once they are advanced or reverse cognitive decline to restore normal cognitive function. Second, there's little awareness in the medical community about CTX, and this leads to delayed diagnosis and the extended diagnostic odysseys we've heard from so many of today's speakers about. This in turn means some patients will have already suffered significant complications that are challenging to address. We need to promote greater awareness in earlier diagnosis. Earlier diagnosis could come with newborn screening, and also with adding the CTX gene to multi gene panels, diagnostic panels, when testing for a cause of the signs and symptoms that occur with CTX. Third, there are too few experts in CTX to manage the patients or even to be available to healthcare providers with little experience with CTX who find themselves caring for a CTX patient to help answer their questions about CTX.

Bob Steiner, MD (03:33:04):

Fourth, excepted treatment is currently, as you've heard, only available for off label use. This can lead to delays in obtaining and maintaining access to the medication for patients as insurance, health plans and or Medicare may not approve it immediately, or may later declined to cover it. Losing access to the medicine can have devastating consequences for patient's health. So finally, Nell and Kim, thank you for the opportunity to participate in this meeting. It is a critically important venue for us all to learn how to better address the CTX community's needs.

Kim McCleary (03:33:47):

Thank you, Bob, for such a comprehensive list and understanding of many of the areas in which more options and better policy could help ease patients burdens and perhaps circumvent some of the heartache that we've heard about today. I want to offer Holly, Estefania, and George to add anything you think is missing from Bob's list so that we have it as part of the conversation today. I know I'm putting you on the spot. It's a tough question. You did such a good job. Anything come to mind? Nell, you're welcome to weigh in as well here.

Neel Odedara (03:34:33):

So, I do want to share a perspective just relating to were talking about concerns with coverage. We have a comment those submitted online. So, Sue who joined us earlier from Oregon, wants to share her story. Because her son Eric is so severely disabled, he's covered by Medicare and Medicaid. His Medicare Part D is covered by the state of Oregon. About five years ago, the Medicare Part D provider, he has then took Chenodal off their formulary. This was very sudden. And since the state of Oregon was involved, it was very complicated to get a new Medicare Part D provider. This was very frightening. And Sue mentions, "I was in tears as I made numerous calls to the state of Oregon to get his Medicare Part D changed to a new provider. It was very close to the cutoff date before Eric's Medicare Part D was changed." The fact that Chenodal coverage is left to the whims of Medicare Part D providers is frightening to family members.

Kim McCleary (03:35:36):

That's certainly something we heard across the conversations and planning for today is just how capricious it can be. And one community member shared that she just plans to spend her Christmas and New Year's holiday fighting with her insurance company, because that's when they make the decisions about whether the medication will be covered for the next calendar year.

Neel Odedara (03:36:00):

And I think, especially when we take it in the context of some of the stories we've heard aboriginals in particular around just the devastating effect of disruption in treatment. I think really just underscores the how important this issue is.

Kim McCleary (03:36:24):

There have been also some comments submitted and conversations we've had just as we think to other ways in which the treatment burden might be lessened. Say for instance, a longer acting form of Chenodal was mentioned by one community member or taking it in some other form, especially for the young kids. As we heard from Kay and others this morning, just the burden of those extra doses and mixing the formulation for the kids, and that uncertainty as they grow when their body size changes of knowing whether you've got the right amount were enough medicine going in. So those perhaps are ways in which innovation could help reduce the treatment burden that patients experience.

Neel Odedara (03:37:15):

Absolutely. And I think that speaking to some of those unmet needs, we have some comments, additionally that have been shared. So we have Alicia, who's a mother of a CTX patient from Massachusetts. She mentioned that finding a medication to stop CTX from progressing is an urgent priority. We need help with the side effects, including problems with eating, problems with speaking, and kidney stones that are formed every six months. We have Maria, a caregiver mentions her son is seven years old and has been recently diagnosed. She'd like to know of other cases of diagnosis at that age and their evolution with current treatments. So I think that additionally being able to further understand with the long-term impact of CDCA, if and how treatment needs to be adjusted with variation and progression in symptoms. I think are all key uncertainties that we're hearing about.

Kim McCleary (03:38:26):

And certainly Bob's point about better education of healthcare professionals across the spectrum so that when even individuals diagnosed with CTX have other medical needs, they don't constantly in the process of re-explaining what CTX is, why they're on the treatment, how this factors into maybe the other difficulties they're experiencing in addition to certainly the need to better educate professionals in the service of getting people diagnosed and treated earlier and sooner. With that, I'm going to thank our panel Holly, Estefania, George, and Bob, for being with us today. And we're going to just summarize some of the themes today that you and other members of the community have brought forward. So thank you so much for being a part of this meeting and for sharing your perspectives, and your courage and commitment to advancing change on behalf of the community.

Estefania Amyerich (03:39:27):

Thank you.

Neel Odedara (03:39:29):

Thank you all.

Kim McCleary (03:39:40):

With that, there is an opportunity now maybe to reflect and get some additional comments that are coming in through the comment form. And please, if you have additional things you want into the record, even if we don't have a chance to get them in as the time ticks away toward the end of the meeting, we want to have them for the voice of the patient report. So you can use that common form on the same web page that you're viewing the meeting on right now. It's really so compelling to understand that what we've heard today, it's really a shift from what is in the medical literature, just about the age at which CTX can present. And often I think it's at least published that there's an onset in the late teenage years or the early 20s, or even the 30s, but we've certainly heard many experiences today that begin right at birth or shortly thereafter.

Kim McCleary (03:40:43):

And so, we're brought back to this idea of maybe there are different forms of CTX, an early infant form, and one that may not present itself until later. And just the opportunity for things like cataracts and the xanthomas to be a real red flag to the professionals that would treat those conditions and see them. Holly just said moments ago that her cataracts at a young age were just waved off as an outlier, and how many people could be saved and improved if that weren't the case. If not just being dismissed as not

being important and just testimony after testimony about the benefit of earlier diagnosis and earlier treatment and the impact that can make in terms of a better life for that individual.

Neel Odedara (03:41:45):

Absolutely. And I think with that in mind, I also do want to share just a few more additional comments that we're receiving from folks who have joined. Again, just to underscore, if you do have the opportunity to call in or share additional comments, it is important to get that your voice in the record, that number again is 703-844-3231. I think, it seems like we have gotten some additional comments. Fortunately we've heard from Avryle in the UK, she's mentioned that malnutrition has created osteoporosis. This has caused femur breaks and led to surgery with adding metal plates and screws. Nutrition should be addressed over the course of the life of a CTX patient. Some of the greatest worries they have are the supply chain or availability of CDCA being interrupted to the UK, which is a death sentence for CTX suffers, who deteriorate rapidly.

Neel Odedara (03:42:53):

We also have Catherine from New York sharing that it was said that gait and balance issues cannot be corrected by treatment. If one has not yet developed these issues with, will CDCA prevent one from developing them? I think that certainly these comments, I think I and Kim came with what you were just mentioning around a need for better understanding of the progression of CTX, the different types that may form, and then different variations and treatment needed if with that understanding to help patients navigate. I think, especially as you consider the degree of uncertainty, the uncertainty involved and how that may impact just how it is that as a caregiver, your best able to support your afflicted family members.

Kim McCleary (03:43:50):

Absolutely. It is just profound, the number of research questions that remain unanswered about CTX and how lives could be improved if we had a better understanding of all of these features. Well, we have reached the point in the meeting where we are eager to hear from Dr. Vijay Kumar from the US Food and Drug Administration. This meeting has been held in collaboration with the FDA, and we're grateful for your colleague, Will Wallen's help as we planned over these past months for today's meeting. So it feels very momentous that you're here with us now and able to share with us what you've heard from the CTX community, and how the FDA will make use of this information that patients have so courageously shared to inform regulatory decision-making and hopefully a brighter future for more therapy options for CTX patients going forward. Dr. Kumar, we're pleased to have you with us.

Vijay Kumar, MD (03:44:58):

Thank you, Kim and Nell. Good afternoon. I am Vijay Kumar. I am a Clinical Reviewer in the Office of Tissues and Advanced Therapies within the Center for Biologics Evaluation and Research, better known as a CBRE at the FDA. I want to thank you for providing me an opportunity to share the FDA's perspective on the Patient-Focused Drug Development. I would like to thank the organizers for putting together a very informative meeting on CTX with broad representation in the audience, from people who are afflicted with CTX, their family, caregivers, academic researchers, rare disease, advocate, and the participants from the life science industry and healthcare professionals. Today, we heard some fairly powerful testimony from people who are living with CTX, their family, and their caregivers. I want to thank and commend the participants, both for taking the initiative to educate us and also for making the

commitment to improving the care and possibly find a cure for those who are afflicted with CTX. Can we go to the next slide?

Vijay Kumar, MD (03:46:38):

I have no conflicts to disclose. And this presentation reflects my views, and it does not bind or oblige the FDA. Next slide, please. The Food and Drug Administration, FDA recognized the need for systematic ways of gathering patient and caregiver perspectives about their conditions and the different treatment options. The reason we are interested is that as people who are living with this disease, you are experts on what it is to live with this disease. You can articulate specific disease features, and also how it impacts your day-to-day functioning and the overall life impact in very, very concrete tubs. As we began the day, Dr. Duell excellently outlined the various critical features and the treatment options for CTX. Then we heard from all of you bring to life, what it means to live with many of the clinical features of CTX. So for every clinical feature that Dr. Duell mentioned, you brought more information, whether it is chronic diarrhea or cataract or xanthomas, cognitive, and neurological challenges.

Vijay Kumar, MD (03:48:22):

You also described the long journey to diagnosis, and the average diagnosis is done only in the third or the fourth decade of life, and the toll, the delayed diagnosis and multiple doctor visits took on your family. You also described the emotional toll that is seen not only that is experienced, not only by people who have the diagnosis of CTX, but also by the parents, by the spouses, by the siblings, and the caregivers. This must have taken a lot of courage to share your personal stories with a worldwide audience, and we cannot thank you enough.

Vijay Kumar, MD (03:49:21):

So, for some of you who are not familiar with what exactly is patient- focused development. Can we move to the next slide, please? We want to understand what are some of the burdensome aspects of living with the disease that can be targeted in our academic and research institutions for developing products. Then when it comes to the clinical studies, this will help us design better clinical studies recruit potential patients, and also retain the study participants. So at that time, when the studies are submitted to the FDA for review, the education you have provided will help us better assess the benefits and risks of the various medical products and integrate into our thinking, how these assessments align with the outcomes, and the preferences that are considered very meaningful by the patient community and by the caregivers. And once the studies are ongoing and the products are approved, it also helps us to better communicate with both the patients and their healthcare providers to make an informed decision making on all the different treatment options that they have.

Vijay Kumar, MD (03:51:11):

Next slide, please. FDA has made a commitment to a rare disease activity and the three centers of the FDA, the CDER, CBER, and CDRH. Each center has a rare disease coordinated activities. We have Rare Disease Council meeting, and Rare Disease Training for all clinical reviewers like me. We also externally engage with the patients and the advocacy groups through the patient-focused drug development meetings and the Voice of the Patient Reports. We participate in Photo and Video Projects, and Patient Listening Session.

Vijay Kumar, MD (03:52:10):

Can we go to the next slide, please? Furthermore, we are a part of the Bespoke Gene Therapy Consortium, which is a public private partnership, including CBER, the center for drug evaluation and research has created a Rare Disease Hub with the Division of Rare Disease and Medical Genetics. When we top off rare disease are often designated products, we are talking of diseases that have an annual incidence of less than 200,000 people within US. And as you can see in 2020, 31 out of the 53 drugs that were approved were often a disease designated, and two of the five biologicals that were approved were for rare diseases. We also have had a device approved for Humanitarian Device Exemption. So as you can see all three centers, CDER, CBER, CDRH are committed to work with the rare disease community.

Vijay Kumar, MD (03:53:25):

And then the next slide, please. I'm sure the CTX community is galvanized by today's event. As Bob Steiner mentioned, there are no approved treatments for this disease. To build on this momentum, please consider taking projects like natural history studies or developing patient registry programs. Again, I would like to thank you for inviting me to this event. I look forward to continuing the conversations and my contact information and links to agency resources and reference documents are listed on the slide. Thank you.

Kim McCleary (03:54:25):

Thank you so much, Dr. Kumar, for being with us today. And it's clear how intently you were listening to the voices of the CTX community members in the way that you reported back on what you heard to be the challenges, the opportunities, and the hopes and aspirations of the community. We appreciate you also putting today's meeting into the context to how you and your colleagues at FDA might consider what they've heard today as they review different sponsors applications for clinical trials and for new medicines and therapies that might come through the agency. So again, we're appreciative of the collaboration that we've had from the FDA and the opportunity to have this forum to bring the CTX communities voice to you and your colleagues at the FDA. Thank you so much. And now, I'd like to invite Robert Rauner, the President of the United Leukodystrophy Foundation back to help us close out today's session. And, Bob, I know you've been listening intently as well, and I'm eager to hear your closing remarks as we wind up our time together today.

Robert Rauner (03:55:46):

Oh, yes. Thanks, Kim. This has been very enlightening meeting. I've met many of the CTX families over the years, so it's heart wrenching to hear the stories that were told. And I know it takes a lot of challenge to come to a meeting like this and bare your soul, and they've done a great job. And I think everybody's got a really good idea of what the challenges are for these families going forward. So I'm pleased with that, this meeting has gone today and I hope that the Food and Drug Administrations, and other people learn a lot from this meeting today. So all I can do is, especially to thank the speakers, our partner organizations, all the panelists and all the participants, we couldn't have done this without you. Of course, I would be remiss if I didn't a special thank you for Kim and some of the kit collective for their work to bring a CTX Patient-Focused Drug Development Meeting here to our friends here at the Food and Drug Administration.

Robert Rauner (03:56:55):

So the other people we really want to thank our sponsors, career therapeutics, [inaudible 03:57:02] for their support on this meeting. We could not have done this without their help and support and all the

work they've done to support the families that are affected by CTX. So we have a very large thank you for them. We also want to thank the Food and Drug Administration for this forum and partnership and my cooperation. This has been the best event that's happened over the last several years for the rare disease family. So we really thank you. Especially we want to thank William Wallen. He has been assisting us and guiding us in this whole process to work with the Food and Drug Administration, and he' helping make this Patient-Focused Drug Development Meeting a success. Just a couple little things, the comment form will be available at ctxresources. org forward/unlockCTX until October 14th for the community members.

Robert Rauner (03:58:07):

You can submit some additional thoughts, view points and experiences that today's meeting might bring to mind. So please, reach out, and if you got something we'll get in there. I think it's real important because our voice of the patient report will come out in a few months and those will be included in that patient report. So please, get those in as soon as you can. Our recording of today's meeting is going to be posted on the same link after the meeting has ended today. So if you want to start going back to it, that would be great. Share with other people that you may know may have missed the meeting and making be with this meeting. Obviously, this is a very exciting time for the CTX community, [inaudible 03:58:55] continued commitment to the community and the emergence of the CTX Alliance, nonprofit as an organization that's dedicated to advancing the needs of the CTX patients we heard so clearly from today. Again, thank you everyone that participated in this meeting today. So with that, I will turn it back to Kim and Nell, in the studio for final comments.

Kim McCleary (03:59:22):

Thank you so much, Bob. And thank you for your leadership of the United Leukodystrophy Foundation and your partnership with the CTX community over many years, but particularly leading up to today. And you are part of the success of this meeting. So thank you for your leadership and guidance as we prepared for today and carried it out from beginning to end. Thank you.

Neel Odedara (03:59:49):

Thank you.

Kim McCleary (03:59:51):

Nell, I also want to say thank you to you for bringing your family's experience through your sister's testimony earlier in your own comments throughout the day. And for taking time away from family and work responsibilities to join me here in the studio, it's been a more pleasurable experience having you by my side and learning from you along the way as well. And I also want to thank the entire team. A lot of folks around us that made this broadcast possible.

Kim McCleary (04:00:17):

And all of the patients, family members, advocates that have participated in huge ways as so many others have said, "What courage it took to share your story so powerfully, so viscerally, so personally, so vulnerably, so that the experience of living with CTX can be better understood, appreciated, and grappled with, as we all work together for change in progress in the future." And with that, I'll close out today's meeting and wish everyone a good evening, a good afternoon, a good morning, depending on where you're joining us from. And we look forward to continuing to receive the community's comments

through the comment form and to sharing the voice of the patient meeting report with you in the coming months. And with that, I'll say thank you and good day.

Neel Odedara (04:01:14):

Thank you. Thank you everyone.

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