Voice of the Patient

Report from the Patient-Focused Drug Development Meeting on Cerebrotendinous Xanthomatosis (CTX) Held on September 14, 2021

UNLOCK CTX

CEREBROTENDINOUS XANTHOMATOSIS

An initiative of the United Leukodystrophy Foundation

Organized & Hosted By:

united LEUKODYSTROPHY FOUNDATION

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FROM THE DESK OF ROBERT RAUNER, PRESIDENT, UNITED LEUKODYSTROPHY FOUNDATION

On September 14, 2021, 92 cerebrotendinous xanthomatosis (CTX) patients, caregivers, advocates, healthcare providers, academic researchers, industry representatives, and government officials came together for the Unlock CTX Externally-led Patient-Focused Drug Development (EL-PFDD) meeting to make the voices of the CTX community heard. Eighteen community members shared how CTX has affected their lives. On behalf of our patient community, their families and caregivers, thank you for your commitment, participation, and support!

In 2007, the United Leukodystrophy Foundation brought on the first board member who has a family member with CTX. That is when we began to learn more about CTX and began to create opportunities for increasing knowledge about CTX. We made a small grant to Dr. Andrea DeBarber at Oregon Health and Science University to support her CTX research. We held CTX-specific meetings at our conferences and hosted an international meeting to explore what would be required to add CTX to the Recommended Uniform Screening Panel (RUSP) for newborns in an effort to aid earlier detection and diagnosis. Over the past year we have been working with the CTX families to plan and host the Unlock CTX PFDD meeting and have helped them to form an independent nonprofit organization named the CTX Alliance.

The Unlock CTX PFDD meeting for cerebrotendinous xanthomatosis was one of the first opportunities for CTX patients and family members to share their lived experience with the broader medical and regulatory community. This was truly a milestone for our community. It also served as a testament to the power of individual patient advocacy groups to come together to benefit our disease community. The meeting was the culmination of nine months of planning and collaboration by the patient advocacy groups facilitating this meeting.

We were grateful for the opportunity to amplify our collective voice for our distinguished guests from the U.S. Food and Drug Administration. I want to thank Vijay Kumar, M.D., Office of Tissues and Advanced Therapies, CBER, FDA for his remarks on the value of patient-focused drug development in CTX and themes heard from the CTX community. We want to offer a special thank you to William Lewallen, FAC-P/PM, for his help throughout the planning process to guide us from the FDA perspective, so we would have a successful EL-PFDD meeting. We also thank P. Barton Duell, M.D., Professor of Medicine, Oregon Health and Science University, for his "Overview of the Diagnosis, Clinical Features, and Treatment of CTX" that helped provide a strong foundation for the meeting.

We express our deepest appreciation to Kim McCleary and Samantha Mayberry from The Kith Collective for all of the work they did to make this EL-PFDD a success. Their attention to detail helped us to have a very smooth meeting that was meaningful to everyone who participated.

Our patient families brought their voices to help us better understand their experiences, their struggles, and their hopes. Courageous panelists put their energy into action and made a choice to share their perspective of certainty, amidst a path of frequent uncertainty. We want to acknowledge the following organizations that have been our partners in this effort: Alex, The Leukodystrophy Charity, CTX Alliance, European Leukodystrophies Association, Hunter's Hope Foundation, Leukodystrophy Australia, Leukodystrophy Resource and Research Organisation, and the Spanish CTX Association.

Lastly, we want to thank our generous sponsors, Travere Therapeutics and Leadiant Biosciences.

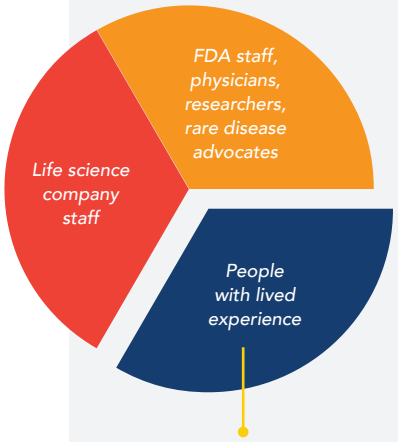
Thanks, all, for your tremendous support and commitment.

Robert Rauner

Robert Rauner, President
United Leukodystrophy Foundation

> ***This was truly a milestone for our community. It also served as a testament to the power of individual patient advocacy groups to come together to benefit our disease community.***

92 participants in the "live" meeting



- *People diagnosed with CTX*
- *Family members of people diagnosed with CTX (parents, spouses, siblings, children, grandparents)*

Community Presenters

Estefania Amyerich, speaking on behalf of sisters Lourdes and Nuria (Spain)

Bobbi Blanchard, speaking on behalf of son Jordan and daughter, Joelle (Wisconsin)

George Bryce (North Carolina)

Shannon DeLaMar, speaking on behalf of son Alex (Illinois)

Avril Dimond, speaking on behalf of mother, Anne (who subsequently passed away in December 2021), and her late aunt, Gilly (England)

Kay Fischer, speaking on behalf of sons, Jacob and Herman (Norway)

Narinder Ghara, speaking on behalf of son Sarabnoor (New York)

Robin Huard, speaking on behalf of son Duane (Washington)

Thomas Johnson, speaking on behalf of wife, Debra (North Carolina)

Austin Larson, M.D. (Colorado)

Shawn Laurie, speaking on behalf of husband, James (Texas)

Sangna Odedara (Virginia)

Holly Rosengrant (Illinois)

Bob Steiner, M.D. (Wisconsin)

Sue Stewart, speaking on behalf of son Eric (Oregon)

John Wolf, speaking on behalf of daughter, Ashley (Oregon)

Catherine Zonsky (New York)

EXECUTIVE SUMMARY

Cerebrotendinous xanthomatosis (CTX) is an ultra-rare disease first recognized in the medical literature in 1937. It is caused by an inborn error of metabolism, a mutation in a gene called CYP27A1. Members of the global CTX community joined together for the first time to describe the effects of CTX on their lives, the burdens of the disease and its treatment, and unmet needs in a meeting convened as part of the U.S. Food and Drug Administration's Patient-Focused Drug Development program.

Seventeen community members from the U.S., England, Norway, and Spain prepared in advance to articulate their experiences and expectations. (See sidebar at left.) They included individuals diagnosed with CTX, parents of children, teens, and adults diagnosed with CTX, spouses and siblings of people diagnosed with CTX, a caregiver of a parent diagnosed with CTX, and professionals who are also community advocates. Collectively they represented a broad range of experiences, from the earliest known diagnosis of CTX to one of the oldest known living patients. There were several families with more than one member living with CTX and disease severity ranged from mild to extremely severe impacts on daily life. Existing treatments were reported by some to be relatively effective at managing symptoms, while most others have serious and urgent unmet medical needs.

Greatest Burdens

Diagnosis – For many of those who spoke or provided written comments, the process of getting an accurate diagnosis was a lengthy and frustrating process with serious consequences for the life of the affected individual. Some parents reported noticing symptoms as early as days or weeks immediately following birth, but diagnosis was often delayed by years and even decades. For others, symptoms began in early adulthood with the appearance of strange growths, later identified as xanthomas, and the diagnosis came as somewhat of a surprise. Still others experienced worsening gastrointestinal, neurological, behavioral, or mobility issues as teens or adults that eventually led to diagnosis of CTX. Frequently, severe, irreversible progression of the disease had already occurred by the time of diagnosis. Looking back, many individuals could cite missed opportunities for earlier detection and diagnosis, especially those with a history of early-onset cataracts.

Symptoms – There are a large number of body systems affected by CTX and symptoms experienced at different stages of life. Along with cataracts, participants identified chronic diarrhea, failure to thrive, and developmental delays as some of the symptoms that first prompted medical attention. Difficulties with cognition, communication, mobility, balance, and coordination were among those that imposed the greatest burdens. Tremor, seizures, joint pain, musculoskeletal abnormalities, osteoporosis, bone fractures, and xanthomas on the tendons of the hand and ankle were symptoms that presented immediate difficulties and often became more pronounced with age. A few participants described autism-like complications, including severe communications and intellectual challenges that presented at an early age and rendered an individual unable to function independently. Depression, anxiety, and behavioral issues added to the overall burden of CTX for both the patients and their caregivers.

Impacts – The effects of these symptoms were profound for many of the meeting participants, in terms of physical, intellectual, and emotional functioning. Some of the individuals diagnosed early in life or quickly following the appearance of symptoms reported less severe impacts. Caregivers and families were also deeply affected by the experience of CTX. Parents, siblings, spouses, and children described the emotional, social, and financial tolls of caring for someone with CTX. Feelings of fear, helplessness, guilt, anxiety, depression, strains on marital and family relationships, and negative influences on work performance, educational and career attainment and family dynamics were repeated over and over throughout the meeting. The issue of testing other blood relatives for CTX presented additional challenges for some families.

> *"Looking back, many individuals could cite missed opportunities for earlier detection and diagnosis, especially those with a history of early-onset cataracts.*

Treatment and Managing CTX

Once diagnosed, individuals with CTX rely heavily on treatment with chenodeoxycholic acid (CDCA), approved for use in treating gallstones and used clinically (off-label) as a replacement therapy in CTX. Since the most-used medication to treat CTX is prescribed off-label, accessing quality care can be an added challenge. Participants reported benefits from CDCA upon initiation of treatment, chiefly slowing progression and reducing frequency or intensity of some symptoms, especially gastrointestinal issues, tremor, balance and coordination problems, and some of the cognitive impairments. However, not all symptoms improved with CDCA, especially mobility problems, severe autism-like features, bone-related issues, and mood and behavioral symptoms. Those whose CDCA treatment had spanned many years reported a sense of reduced benefit from the medication over time and interruptions in treatment led to functional losses that were not fully regained when treatment resumed. Other burdens associated with CDCA included the multiple daily dosing regimen, uncertainties about dosing levels for growing children, and major challenges with access due to its off-label use and supply-related issues over the years.

Symptomatic medications prescribed both before the diagnosis of CTX and to supplement CDCA after diagnosis were reported by participants to have varying levels of effectiveness, depending on the nature of the symptom being treated and the response to it. Antidepressants and anti-anxiety medications were the drugs most frequently cited by participants, following CDCA.

Surgical treatment to address cataracts and other vision-related problems and to remove xanthomas were reported by several participants. They also noted frequent complications arising from these procedures.

Participants reported use of several types of supportive therapies in pursuit of improved function and quality of life, most frequently physical, speech, and occupational therapy, used alone or in combination. Chiropractic treatment, attention to diet, and reliance on assistive devices were used by some participants as well.

Looking Ahead

There are many gaps in the scientific understanding of CTX and many unmet needs in the care of children and adults living with CTX. It is widely recognized that early diagnosis and treatment can serve to decrease the impacts of CTX. A near-term possibility, referenced by several participants as a source of hope for future generations, is newborn screening. The community embraces this as a high priority and researchers are working to complete a series of required steps to get testing for CTX added to the Recommended Uniform Screening Panel (RUSP).

Participants also expressed high priority for getting CDCA therapy approved for the treatment of CTX. This was seen as a means to improve initial and sustained access to therapy, as well as an advance that could lead to better education of physicians about CTX and therefore better care.

The third major priority articulated at this meeting was the need for additional therapy options that better treat all the symptoms of CTX, reverse its effects, reduce the burdens on patients and families, and – ultimately – address its root cause. Some pointed to advances being made in gene therapies as a major hope for the future.

This first-of-its-kind meeting for the CTX community was itself a source of hope for the future. Individuals benefited from the opportunity to learn from others with lived experience and strengthen ties. The shared priorities identified at this meeting are giving rise to new initiatives and a new spirit of empowerment.

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SECTION 1:

INTRODUCTION TO THE UNLOCK CTX MEETING

Cerebrotendinous Xanthomatosis (CTX)

Cerebrotendinous Xanthomatosis (CTX) is an ultra-rare, recessive genetic disease that affects the body's ability to metabolize fats known as sterols. A defect in both copies of the *CYP27A1* gene results in decreased bile acid synthesis and accumulation of cholestanol in the plasma and body tissues. Lesions called xanthomas may develop on tendons and/or in the brain. Individuals with CTX experience a vast range of symptoms that progress across the lifespan, with increasing severity and impact on daily functioning, health, and well-being. Symptoms may begin in infancy, yet the disease is often not identified until neurological symptoms become more pronounced. Despite numerous means of detecting and diagnosing CTX, the average age of diagnosis is 35. This long delay in diagnosis and lost opportunity for earlier treatment can have tragic repercussions. While there is no cure for CTX, if it is identified and treated early, progression can often be slowed or stopped.

"Hello and welcome to the Unlock CTX patient-focused drug development (PFDD) meeting on cerebrotendinous xanthomatosis, or CTX. My name is **Kim McCleary** and I will be moderating today's meeting along with **Neel Odedara**. To lead off today's meeting, we'll hear 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."

Thus began the broadcast of the four-hour virtual Unlock CTX meeting, originating from a studio in Falls Church, Virginia, just outside Washington, D.C., and connecting community members from across the United States and around the world by video, telephone, and written comments submitted in real time.

Kim introduced Neel, whose credentials for his role in the meeting stem from both professional endeavors and, perhaps more importantly, from his experience as the younger brother of **Sangna Odedara**, who was diagnosed with CTX at age 33 after a lengthy diagnostic odyssey. "Sangna's diagnosis has had a profound impact on my family, and it seems like every day we are navigating the unknown implications of CTX. It's our hope that today's discussion will be an engine to drive further understanding of CTX," Neel declared. Kim added her hopes for the day, as well. "I hope this meeting will be a catalyst for connection and community building and that your voices will gain strength through unity. As I've come to know many of you through our preparations for today, I have been inspired by the resolve and resiliency with which you lead your lives. I know how important those qualities are to effective advocacy for change," she said. (Learn more about Sangna's experience beginning on page 10 and read brief bios for Neel and Kim on page 30.)

These opening remarks were followed by an overview of the clinical presentation and treatment of CTX provided by **P. Barton Duell, M.D.**, Professor of Medicine at Oregon Health and Science University. Dr. Duell began with an acknowledgement of the tough path that people and families affected by CTX must travel. "I have been interacting with and providing care to patients with CTX for about 30 years. Every patient's journey is different, as you'll hear today. Many feel alone and afraid. There are so many unknowns when they find out they have CTX, just as Neel said. So, forums like this one are excellent for helping to spread valuable information and to help people better understand what's going on with their condition." (Dr. Duell's presentation begins at 0:26 minutes on the recording.)

The meeting was structured in two parts, the first dedicated to understanding the burdens associated with CTX, including the often-lengthy process of obtaining a correct diagnosis, the symptoms that patients experience, and the toll these symptoms take on the individual and the family. The second segment was dedicated to the current treatment for CTX, aspirations for expanded treatment options, and the unmet needs of the community. Recorded statements relevant to each topic led the two segments, followed by a

panel of other community members who dialogued with the moderators. Additional community members phoned in during those discussion sessions, and the moderators read written comments aloud, as well. See the meeting agenda on page 31.

Before turning to the first set of recorded remarks, Kim provided further context to set the tone. "In the setting of PFDD meetings, I want to firmly state that the individuals living with CTX and their family members are the experts in the discussion we'll have today. I wish to honor and recognize the courage they demonstrate in being asked to recall and relive difficult experiences and memories. Each person deserves our respect and compassion for all they have lost to CTX and the bravery it takes to speak in a forum like this. Now let's hear first from **John Wolf**, who many know and consider to be the 'godfather of CTX advocacy.'"

"I've been involved in raising awareness and engaging in advocacy for CTX since my daughter, Ashley, was diagnosed with CTX in 2004," John began. "Over the past 17 years, we have seen some progress, but as you'll hear from other community members today, there are still a great many needs. 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 and better care, and to bolster efforts that will someday lead to a cure." John's experience with his daughter's diagnosis opens Section 2 of this report.

Following the final discussion segment, **Vijay Kumar, M.D.**, provided comments about the U.S. Food and Drug Administration's (FDA's) interest in PFDD as it applies to CTX. Dr. Kumar is a nephrologist who serves as a Medical Officer in the Office of Tissue and Advanced Therapeutics (OTAT) at the Center for Biologics Evaluation and Research (CBER) within the FDA. "When CTX 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. It will help 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 caregivers. 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 so they can make informed decisions about the different treatment options that they have." He concluded his remarks with this request of the community: "I'm sure the CTX community is galvanized by today's event. As was mentioned, there are no treatments approved specifically for CTX. To build on today's momentum, please consider taking on projects like natural history studies or developing patient registry programs," Dr. Kumar urged.

The community was also invited to submit written comments through October 14, 2021, and comments received have been incorporated in this report. In addition, a one-hour community "Family Forum" was held on September 23, 2021, to share reflections and potential next steps for the community. A key theme from that meeting was how much participants learned from one another and how the Unlock CTX meeting helped them feel less alone in their individual experiences, a testament to the very spirit of "community."

"A key theme from that meeting was how much participants learned from one another and how the Unlock CTX meeting helped them feel less alone in their individual experiences.

Patient-Focused Drug Development & the Unlock CTX Initiative

In 2013, the U.S. Food and Drug Administration (FDA) began holding a series of meetings to hear directly from patients, caregivers, advocates, and other key community stakeholders about what it's like to live with various medical conditions and how well available treatments are meeting patients' needs. This meeting series, called the "Patient-Focused Drug Development" initiative or PFDD, has now been expanded to enable patient organizations to host PFDD meetings in collaboration with the FDA. There have been nearly 80 PFDD meetings held to date; approximately half of them have been dedicated to rare diseases like CTX. (See http://bit.ly/FDA-PFDDinfo)

In February 2021, the United Leukodystrophy Foundation (ULF) applied to host an externally-led PFDD meeting on CTX. The FDA saw value in the proposal in March 2021, encouraging participation beyond the United States and the inclusion of individuals and families living in other countries. The meeting and this report are the culmination of a year-long effort by ULF and the CTX community.

The purpose of PFDD meetings in general and the Unlock CTX meeting in particular is for FDA staff, researchers, and developers of drugs and medical devices to understand more fully the burdens of living with a particular medical condition, as well as what patients most value in terms of treatment benefits and the risks and side effects they are willing to tolerate. An example of how PFDD can benefit people living with CTX is the potential to deepen understanding about all the ways in which CTX impacts people's lives at different points along their lifespan and the unmet medical needs that persist in spite of treatment with available medications.

BEFORE DIAGNOSIS AND TREATMENT

AFTER DIAGNOSIS AND TREATMENT

SECTION 2:

SYMPTOMS AND IMPACTS THAT MATTER MOST TO PATIENTS AND FAMILIES

Laboratory Tests to Aid in the Diagnosis of CTX

- Elevated plasma cholestanol concentration
- Elevated urinary bile alcohols
- Elevated 7α,12α-dihydroxy-4-cholesten-3-one (7α,12α-C4) in dried blood spot
- *CYP27A1* genotype (confirmatory)

Detecting and Diagnosing CTX

There are four laboratory tests that can help or confirm a diagnosis of CTX; however, physicians must first suspect a genetic condition or recognize characteristic features of CTX and/or a pattern of symptoms before they will order tests that aid in making the diagnosis.

Thus, each community member's experience of the journey to diagnosis is unique. Yet, among the community members who participated in the Unlock CTX meeting, there were four distinct patterns for how and when symptoms first presented and the course of events that led to testing and a diagnosis of CTX. The four general journeys as described by community members follow. A novel fifth type of journey – the result of testing of a CTX carrier during pregnancy by amniocentesis – is highlighted on page 10. As described on page 12, the potential for testing for CTX as a routine part of newborn screening presents the possibility that someday this singular experience may not be as much of an outlier as it is in 2021.

John Wolf

Scenario 1: Early-life signs and symptoms leading to a CTX diagnosis during childhood *(depicted in blue on page 9)*

John Wolf led off this session with a forceful statement, "I will tell you up front that we are among the fortunate ones." Looking back, John reported that from birth his daughter, Ashley, exhibited one of the characteristic signs of CTX – chronic diarrhea. Yet, in spite of consulting several specialists including pediatric gastroenterologists, they didn't identify a cause. "The first GI specialist didn't believe Ashley had diarrhea episodes up to eight times a day. Another ran tests for celiac, sprue, Crohn's disease, and other things, which came back negative. That doctor then turned to the possibility we were exaggerating," John said. Ashley developed cataracts at age 10, which led the ophthalmologist to refer them to a geneticist for more tests. Some inconclusive results suggested that Ashley might have Smith-Lemli-Opitz syndrome. Then, a conclusive result and diagnosis with CTX. John described what getting that result meant to him, "For a decade we had been fighting this battle to understand the source of Ashley's difficulties. We finally saw a light at the end of a dark tunnel."

For some, the symptoms and diagnoses piled up before a unifying cause was suspected. As an infant, **Sue Stewart**'s son Eric had more diarrhea than Sue thought was normal, based on her experience with her two older sons, but a top pediatric gastroenterologist waved off her concerns. Although Eric kept pace with early developmental milestones, by age two he had spoken no words and only babbled. Sue recalled the progression of diagnoses that followed. "At 2.5 years old, he was diagnosed with a communications

disorder and at three years old, autism. At age five, Landau-Kleffner syndrome was diagnosed after seizures started. At six, his brain MRIs were showing decreased white matter and increased grey matter and they diagnosed an immune system disorder. At age nine, they added intellectual disability to the list. Even after he developed cataracts at age 11, no one connected that to his other difficulties." By the time Eric reached age 16, he was very ill, and she feared he was dying. "I did a google search using the words 'cataracts and autism.' I discovered that difficulties with cholesterol often presented with these two conditions co-occurring." Sue also learned that one of the main research and care centers was Oregon Health and Science University, not far from their home. She secured an appointment for Eric, and he was diagnosed there with CTX, some 15 years after Sue noticed something was not right.

A sudden, dramatic change in function speeds the process of diagnosis for some children. Joelle, **Bobbi Blanchard**'s middle child, had just finished first grade when she developed a hand tremor, coordination problems, and started to show troubling signs of cognitive decline. Bobbi said the abrupt onset of symptoms helped get the doctor's attention. "Because of the neurological nature of her symptoms, her medical care team knew there was something really wrong and they worked diligently for a diagnosis," Bobbi relayed. Still, it would take a year and a half of progressively invasive testing at three different facilities and six different specialists to finally get a diagnosis via whole exome sequencing, an advanced type of genetic testing. Joelle's health declined during those 18 months. A silver lining of sorts was that Joelle's diagnosis led to her older brother, Jordan, age 11, getting diagnosed, too. "His presentation was more 'typical' of CTX, with prolonged jaundice and chronic diarrhea from birth. He had been diagnosed with Tourette's syndrome, had tics, and experienced severe anxiety. CTX fit Jordan's lifelong symptoms to a T. My kids are two of the few who were diagnosed and treated early enough to make a significant difference in their lives," Bobbi acknowledged.

> *A sudden, dramatic change in function speeds the process of diagnosis for some children.*

Often there is a combination of slowly progressive changes and then a more pronounced shift that spikes concern and medical attention. "Alex went from being a very coordinated kindergartner that could play any ball you threw at him to losing the ability to run and jump by age 10 and losing the ability to ride a bike by age 12," stated **Shannon DeLaMar**. Years of physical therapy and seeing many doctors yielded only a vague diagnosis of double-jointed illness on the right side. "Puberty seemed to turn on more problematic neuropsychiatric symptoms, including obsessive behaviors. A few times a month I'd get a call from school because he was dysregulated and needed to be picked up." This triggered more medical testing which detected high triglyceride levels despite Alex having normal blood sugar levels and being of normal body size. His pediatrician referred them to a geneticist who ran additional tests and diagnosed CTX when Alex was 16.

Blanchard Family

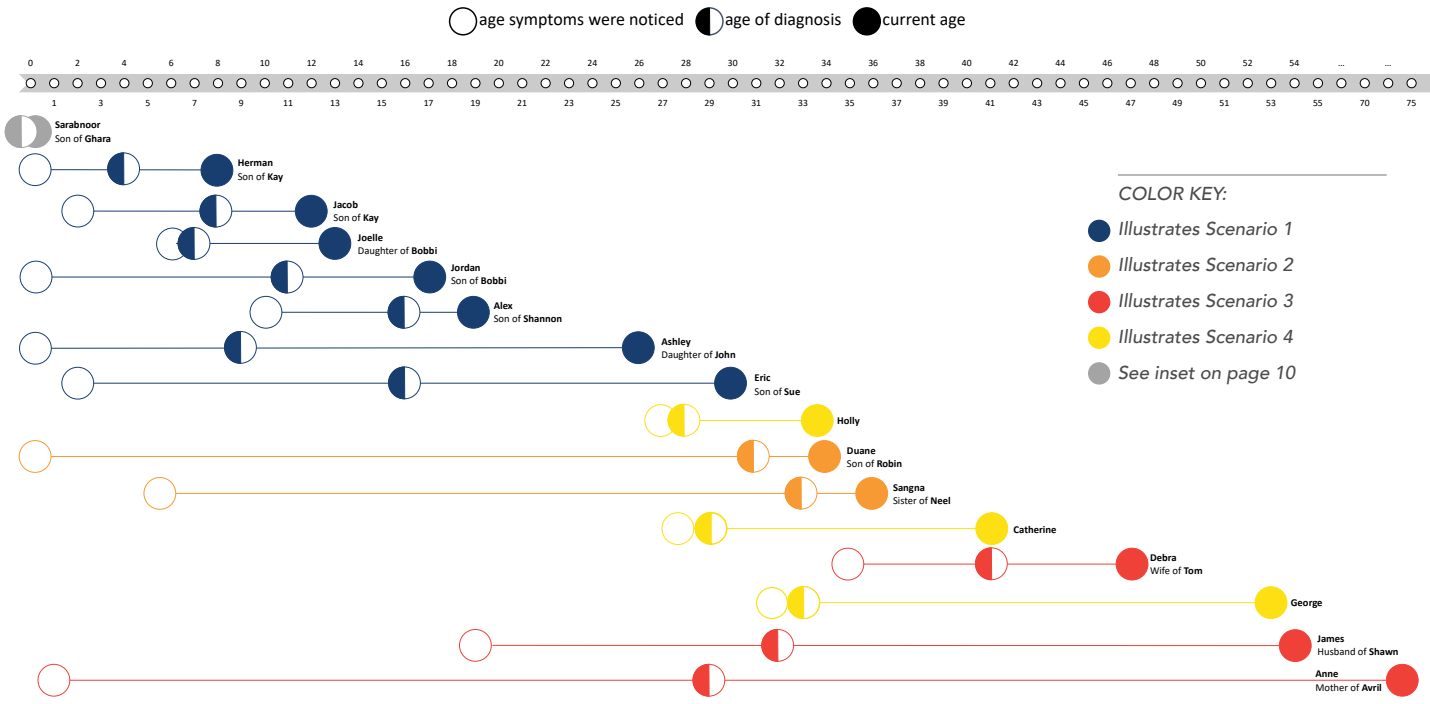


Figure 1: Depiction of the age at which symptoms were first noticed, age of diagnosis, and current age of CTX patients represented at the Unlock CTX meeting.

Common Challenges Across the Diagnostic Odyssey

Each of the individuals who spoke at the Unlock CTX presentation described missed opportunities for earlier diagnosis, which in turn delayed treatment and allowed CTX to progress unchecked. A common refrain among community members was the tendency for primary care providers and specialists to overlook or downplay symptoms and functional impairments. Each person eventually encountered a health care professional curious or diligent enough to do more tests, dig deeper into the medical literature, or make a key a referral. However, they lost precious time, spent resources, and in some cases received potentially harmful treatments.

While each individual's experience was unique, the symptoms or events that most often led directly to a diagnosis of CTX were:

- Early-onset cataracts
- Appearance of xanthoma
- Sudden onset of neurological symptoms
- Sudden change in mood and/or behavior

The Earliest Diagnosis Possible

Narinder Ghara's first son was born in 2011 and had some unusual medical issues that required two surgeries early in life. Doctors wanted to understand his genetic make-up, so they tested him and Narinder. She was found to be a CTX carrier, but she didn't understand what that meant and didn't take it very seriously at the time. When she became pregnant in 2020, her obstetrician made note that she was a carrier of CTX and scheduled amniocentesis at 18 weeks to test the baby for CTX. When the baby's blood tested positive, the doctor counseled Narinder and her husband that it was early enough to end the pregnancy, but they chose to continue. "Now we had to take CTX seriously so we would be ready. We learned about a baby in Israel that was diagnosed and treated very young, so we tried to learn from that family's experience," she said. "It was a stressful pregnancy and we prayed to God all the time."

When her son, Sarabnoor, was born, he had an MRI on day two and his brain appeared to be normal. At two months, he started on a low-dose CDCA treatment mixed with formula in his bottle. "It was hard for him to get used to it and I worried about him getting dehydrated when he wouldn't drink. We worked with the pharmacy and the doctors, and he was tested frequently to monitor his levels. He is five months old now, is reaching a normal weight, and things are getting better. We know we are lucky to have gotten the diagnosis early and see the medicine as a blessing. Our older son has been tested and does not have CTX; he is nine years old now and is doing very well. We hope our story gives other families hope," Narinder said as she cuddled her infant son.

Sangna Odedara

Scenario 2: Early-life signs and symptoms that go undiagnosed as CTX until adulthood (depicted in orange on page 9)

While the four accounts above ended with an accurate diagnosis made during childhood, for others with early-life symptoms, that answer was delayed until later in life. **Sangna Odedara**, age 36, shared her story. "When I was a baby, I had frequent GI issues. My family immigrated to the U.S. when I was six years old. I was always smaller than kids my age and I had difficulty concentrating in school. My parents sought help from various local physicians, but as immigrants living in a small town in rural Virginia, we didn't always have access to the best care," she said. Yet her parents persisted to seek help. "I saw primary care doctors, cardiologists, psychologists, and other specialists, each with his or her own theory about what I had. When no one could find anything, they concluded it was nothing." She had surgery to remove cataracts from her left eye at age 30 and her right eye at age 31, which the doctors found strange, but not sufficient cause for more investigation. By chance, her brother, Neel, had a work project on Parkinson's that led him to think Sangna might have a neuromuscular disorder. He did the legwork to get her enrolled in a study at the National Institutes of Health where testing confirmed the diagnosis of CTX when Sangna was 34 years old. She remembers the impact of the diagnosis. "The news was hard on my family, but it was a relief for me because I finally knew that I had something that I could put a name to."

Robin Huard could relate to Sangna's sense of relief when her son Duane was diagnosed at age 31 after a lifetime of health-related challenges. "We finally had a name to pin his health catastrophe to and it came as a huge relief." She recounted the difficulties that began at birth, when Duane was born a "blue baby" and shortly afterwards required surgery to clear blocked tear ducts. As an infant he had asthma, croup, pneumonia, chronic diarrhea, and an unusual tremor in his hands. As he grew, signs of developmental delay and unusual body movement gave Robin more concern. As with Sangna, Eric, and others, when Duane developed cataracts at age 15, doctors performed surgery but didn't suggest additional testing to determine if his symptoms might have a common cause. A progression of even more serious health concerns plagued Duane in his 20s – a shattered kneecap following a fall; a desmoid tumor on the pad of his foot, which also revealed an unusually high tolerance for pain; enlarged, aching Achilles' tendons, which further impacted his mobility; difficulty swallowing that led to choking incidents, landing him in the emergency room. Robin remembered that harrowing period, "Duane's difficulties with eating were the tipping point. In the span of a few years between 2016 and 2018, Duane underwent a shocking transformation which resulted in his loss of autonomy and having to move back home. His weight

plummeted to 102 pounds; he's near six feet tall. He became weaker and had greater trouble with balance and mobility. The whites of his eyes turned yellow, and he developed kidney stones. He did not remember things and conversations were often repetitive." Robin recounted how Duane's speech changed and how obsessive and anxious he became. His sleep was troubled, and his limbs jerked and spasmed throughout the night. "By 2018 he was weak and wheelchair-bound. He would sit slumped over, mouth ajar, drooling. He spoke very little. He looked like a zombie, and I thought he was dying. We felt helpless and were running out of hope." That's when, with the help of a band of specialists, they got more testing, including genetic testing, and Duane was finally diagnosed with CTX.

Scenario 3: Signs and symptoms that emerge in adulthood and go undiagnosed as CTX for years *(depicted in red on page 9)*

Shawn Laurie's description of the early warning signs of her husband James' changing health status sounded much like Shannon's description of son Alex (see page 9) – except that James was 19, not 10 like Alex. "James and I started dating in college when he was 18. A year later, I noticed that this athletic guy was suddenly having trouble with his balance. He could no longer bicycle or roller skate. He developed enlargements on his Achilles tendons, but he didn't pursue treatment because he didn't have health insurance. Tendonitis followed a couple years later, and severe depression a couple years after that. His therapist encouraged him to get his tendons looked at, which led to a misdiagnosis of MS and treatment with IV steroids. An orthopedist did an MRI on his tendons, which led to more referrals and ultimately the correct diagnosis of CTX at age 31. The active process of getting a definitive diagnosis for James took four years, seven doctors, and multiple therapists and tests."

Debra and Tom Johnson

Debra's precipitous decline took her from a post as a successful president of a manufacturing company with hundreds of employees and active mother of two teenagers to a person unable to work, who slept 14 hours a day and couldn't read a book. It began in 2009 at age 34 with a bout of severe GI pain and diarrhea. Her husband, **Tom Johnson**, described her rapid deterioration that came seemingly out of the blue. "A few months later, in February 2010, Debra was hosting a meeting of executives when she had a major transient ischemic attack (TIA). She got dizzy, collapsed, and had aphasia. They rushed her to the hospital and after spending an evening there, they didn't have any answers. The next TIA came three days later." Within a year, Debra was unable to work. The couple traveled to UNC, Duke, and the Cleveland Clinic in search of answers. Oral steroids were prescribed in hopes of providing some relief. At the Mayo Clinic, an autoimmune neurologist extended her stay to three weeks, ran a slew of diagnostic tests, and brought in 12 other doctors. The diagnosis they made was "autoimmune encephalopathy" and oral steroids were replaced by intravenous pulse dose steroids. She continued to go downhill. More medical consults followed. Without a clear diagnosis, they tried numerous therapies – Imuran, CellCept, Rituxan, IVIG, and Cytoxan – to see if anything would help. Tom continued, "The autumn of 2015 was a low point for us. Debra was 41 years old; we had two teens at home. The trend of her symptoms and her function were both in steep decline. Speaking between ourselves, we felt she would be lucky to see the age of 45. We started looking for research studies and found one called the Idiopathic Diseases of Man study, or IDIOM." It was a cutting-edge genetics study at the Scripps Research Institute that aims to unlock potentially life-saving insights by identifying what disease may be causing the condition. Debra enrolled. "The call we received late on the night of December 29, 2015, yielded a life-saving insight. Finally, we had a diagnosis – CTX," Tom recalled.

Specialists Consulted by Community Members

The often long process to reach a diagnosis involved the following medical specialists across this group of community members (in alphabetical order):

- Allergist
- Cardiologist
- Endocrinologist
- Gastroenterologist
- Geneticist
- Hand surgeon
- Hematologist
- Internist
- Lipid specialist
- Neurologist
- Ophthalmologist
- Optometrist
- Orthopedic surgeon
- Orthopedist
- Pediatrician
- Primary care physician
- Psychologist
- Sports medicine specialist
- "And many other specialists," as several people noted

Scenario 4: Signs and symptoms that emerge in adulthood and are (relatively) quickly diagnosed as CTX *(depicted in gold on page 9)*

Each of the experiences described above are characterized by lengthy searches to discover the underlying cause of a puzzling array of symptoms. However, for other community members, the diagnosis of CTX came as an unexpected shock because it wasn't preceded by debilitating symptoms.

Catherine Zonsky

Catherine Zonsky admits she had a bit of a bad temper in her 20s. One day when she was upset by something, Catherine punched the wall on her back porch. Soon after, a bump formed on the tendon on that hand that delivered the punch. She sought out a hand surgeon to remove the bump and after the surgery he told her that it was more involved than he had anticipated. The mass had grown through the fibers of the tendon, and he had to slice off the top of the tendon to remove it. "I required occupational therapy to regain full function of my finger and hand. To my surprise, within a few years, the bump grew back. When that happened, my parents suggested I consult my father's heart surgeon to see if he could recommend someone who could help figure out what was going on," Catherine said. He referred Catherine to the lipid center at New York University. After an examination and some blood tests, the specialist suspected CTX, having heard about it at a conference. He sent Catherine's samples to CTX specialist Dr. Gerald Salen who put her blood through several tests. "The CTX diagnosis was confirmed and now the bump on my hand had a name, which is xanthoma. I then 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. I credit these doctors with saving my life," she said with gratitude.

Hollisa Rosengrant

This experience resonated with **Hollisa Rosengrant**, also diagnosed with CTX after having a suspicious growth removed from the tendon on one of her fingers. "I was fortunate at the time the growth – which I later learned was called a xanthoma – was the only symptom I had. I did have surgery for cataracts in high school, but that doctor chalked it up to an unfortunate luck of the draw. But when my hand was operated on at age 27, I was truly lucky to have an orthopedic surgeon and team who did thorough research that led them to believe I might have CTX. They referred me to Dr. Duell at OHSU. I traveled to Portland, stayed for tests, and was officially diagnosed with CTX," Hollisa stated.

Update on Newborn Screening Efforts

Many of the tragic consequences of long diagnostic odysseys that lead to treatment delays could be avoided if there was a way to routinely detect CTX at birth or in early infancy. At the meeting, a brief update on efforts to get CTX added to the Recommended Uniform Screening Panel (RUSP) was provided by **Austin Larson, MD**, a physician and researcher in the clinical genetics and genomics group at Children's Hospital Colorado in Aurora:

Austin Larson, MD

"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 (was) made in 2018 to the U.S. Advisory Committee on Heritable Disorders in Newborns and Children. The Committee discussed it in November 2018 and recognized CTX as 'a medically serious condition that deserves thorough consideration.' It provided a written roadmap we are now following to meet the requirements it described.

"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 the Netherlands to test newly collected newborn blood in an effort to prospectively identify a newborn with CTX. We are not sure how many total babies' blood spots will need to be tested before the first CTX case is found, so that will determine how quickly we can re-submit the application and additional evidence to the Advisory Committee.

"The families participating today should know that there are many research groups committed to seeing this through. We are also preparing to have the processes in place to inform decisions about how to manage the care for newborns and young children that may be diagnosed once a test is in use. Thank you for the opportunity to provide this information at this important meeting."

A rather sudden change in physical functioning caused **George Bryce** to seek medical attention at age 33. He related, "I was playing on a church softball team and was having trouble running around the bases. I tripped three times on the way to first base after hitting the ball, so I went to see a sports medicine doctor. He noticed that I had clonus, or muscle spasticity, but he didn't have any answers for me. He sent me to see a neurologist who did an MRI, but he didn't see anything unusual. He referred me to the Mayo Clinic in Arizona. The doctor I saw there examined me and diagnosed CTX right away after seeing the swelling and xanthoma on my Achilles tendon and detecting abnormalities on my spinal MRI. Once I had a diagnosis and learned about CTX, I realized there were signs – like persistent bowel problems – that were missed earlier in my life."

George Bryce

Symptoms Experienced

As the previous section illustrated, there are a large variety of symptoms that individuals with CTX experience across different stages of life. As Dr. Duell noted in the opening clinical overview, "Some people have almost no symptoms and others have every symptom on the list." Symptoms can range from mild to quite severe in presentation and may progress at different rates. Untreated, CTX and its complications can lead to premature death.

Diarrhea and Gastrointestinal Issues

One of the most common presenting symptoms across the lifespan is chronic diarrhea. John Wolf's daughter exhibited this from birth. "While it can sound trivial, caring for her as an infant and toddler was extremely challenging. We changed a lot of diapers, and it became even more complicated when she was potty trained. It was especially difficult when traveling and required making extra stops. Our pediatrician reassured us that she would grow out of it. When she didn't, we consulted specialists, but they didn't help much either," he reported. As stated on page 8, Sue Stewart's son also experienced frequent diarrhea, but a specialist she consulted didn't consider it to be a serious concern. **Kay Fisher**'s younger son with CTX was diagnosed with "toddler's diarrhea" before they understood its root cause. Duane Huard had persistent diarrhea throughout childhood, which Robin described as "greasy, stretchy stools that wouldn't flush properly." **Avril Dimond**'s mother and aunt, both of whom were diagnosed with CTX in their 40s, had lifelong challenges with diarrhea. **Margaret Dennett** of Australia wrote in that her daughter, Dominique, was symptomatic from birth with chronic diarrhea.

Anne and Avril Dimond

Perhaps because bowel problems can be an embarrassing symptom to discuss and the boundaries of "normal" may be hard to judge, some people like George Bryce only connected their early life experience with CTX years later, after getting a diagnosis that helped put it in context (see page 12). GI issues may take other forms as well and may be quite incapacitating. For example, Debra Johnson experienced gastric dysmotility and constant pain, including severe abdominal pain in the upper left quadrant that peaked after every meal. Gas and bloating were problems mentioned by others.

Early-Onset Cataracts and Other Eye- and Vision-Related Problems

A striking symptom reported by many meeting participants (and about 88 percent of CTX patients according to one study[1]) is the onset of cataracts at a younger than expected age, including during childhood. Kay Fisher's older son had surgery for cataracts at age 9. Even at this young age his vision had decreased to 10 percent. Bobbi Blanchard shared her family's experience. "Both Jordan and Joelle required several surgeries to deal with cataracts and additional buildup on their lenses. Oddly, their cataracts appeared at the very same time, at ages 13 and 10, respectively. They had their first surgeries on the same day. The ongoing problems have left them with continually changing vision."

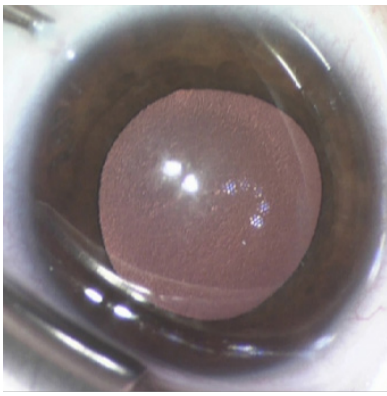


Image of cataract with stippling in the background of the lens that is often seen in patients with CTX. (Courtesy of Barton Duell, MD)

Cataracts were described by John Wolf, Sangna Odedara, Sue Stewart, Robin Huard, and Hollisa Rosengrant in their earlier comments about the path to getting diagnosed. For some, this unusual occurrence was a turning point in that diagnostic journey. In fact, John Wolf referred to Ashley's diagnosis of cataracts as "a blessing in disguise." He explained: "In December when she was age 10, we noticed Ashley was sitting closer to the TV than before. This was especially alarming because she'd been tested at the beginning of the school year, and she had 20/20 vision. Very quickly we took her to the local optometrist to test her again and were told she was now 20/100. Ultimately, this led to her getting a correct diagnosis before CTX progressed into a debilitating condition. It also connected us to the world's leading expert on CTX, the late Dr. Gerald Salen."

[1] *Salen G and Steiner RD. Epidemiology, diagnosis, and treatment of CTX. J Inherited Metabolic Disease 2017;40(6):771–781*

For others, like Duane Huard, no one suggested further investigation to understand the premature occurrence of this condition. His mom, Robin, recalls, "When Duane was 15, he applied for his driver's permit and failed the vision part of the exam. His vision turned out to be quite poor indeed. A visit to the eye doctor revealed he had cataracts, which required surgery. Juvenile cataracts are one of the greatest hallmarks of CTX, and this was truly a missed opportunity for earlier diagnosis. Unfortunately, no follow-up or genetic testing was suggested by either his optometrist or ophthalmologist. Like Duane's persistent diarrhea and shaking limbs, this health issue was somewhat forgotten."

Other problems with the eyes were reported as well. Ashley Wolf experienced a complication related to wound healing after her first surgery. Eric Stewart has had four eye surgeries, including cataract removal at age 12, capsulotomy to treat secondary cataracts, and vitrectomy (to remove and replace the gel-like substance in the middle portion of the eye). Duane Huard had surgery as an infant to clear blocked tear ducts. Later in life when he became extremely ill prior to diagnosis, the whites of Duane's eyes became yellow, a sign of jaundice and abnormal liver function. **Kathy Deaner** sent written comments stating that her 35-year-old son Joe's eyesight is deteriorating.

Dr. Duell highlighted a 2019 study that found three new cases of CTX among 170 individuals diagnosed with bilateral cataracts between the ages of 2 and 21 years. As Freedman et al, report, "These data suggest that juvenile-onset idiopathic bilateral cataracts may be useful as a screening marker for CTX and that ophthalmologists can play an important role in facilitating early identification of this condition."

JAMA Ophthalmol. 2019;137(11):1312-1316.

Xanthomas (Tendinous Growths)

As was stated by Catherine Zonsky and Hollisa Rosengrant above, the appearance of unusual growths on tendons of the hand or ankle can be another outwardly visible sign that prompts medical consultation. This was also the case for Avril Dimond's family members. "Both my mother, Anne, and my Aunt Gilly had physical challenges throughout life. Although Aunt Gilly was younger, by the time she was in her late 30s, her symptoms were more concerning than my mother's. She had premature cataracts, seizures, and other difficulties. But it was the appearance of a xanthoma that led doctors to think about leukodystrophy and ultimately to diagnose her with CTX. My mother was tested too since she had a long history of zig-zag walking, migraines, and other symptoms, and she too was diagnosed with CTX."

Xanthomas can grow quite large and may become inflamed and painful. "My son, Joe, needs help with the xanthomas on his heels and legs that are getting bigger," wrote Kathy Deaner. For others, they are small and may only be apparent to a healthcare professional familiar with them. Catherine Zonsky mentioned that it wasn't until her physical examination by CTX expert Dr. Gerald Salen that she understood the thickness along the back of her ankles was connected to the growth on her hand.

Xanthomas may also form in the brain where they can be detected by magnetic resonance imaging (MRI). Dr. Duell described the image at left in his clinical overview, "This is a case of a xanthoma that interferes with cerebellar function, which is important for controlling motion. People who have cerebellar injury can end up with ataxia, or the inability to move smoothly." Shannon DeLaMar noted her son, Alex, had his first MRI at age 16. "He had white matter deposits equivalent to a 40–50-year-old," she reported.

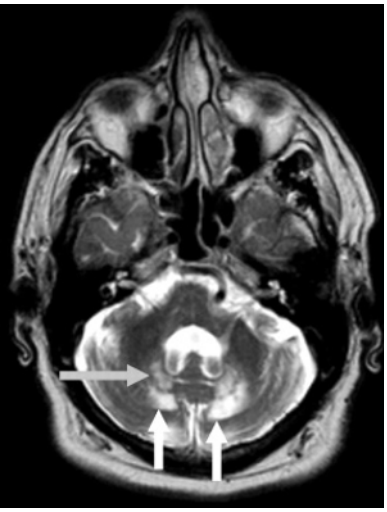


Image from: CTX: A treatable ataxia. C. S. Clemen, et al. Neurology Apr 2005, 64 (8) 1476

Ataxia, Movement and Mobility Issues, Muscle Weakness, and Frailty

Nearly every participant described some type of issue related to balance, coordination, and/or movement. For some, these issues presented at a very young age, like Joelle Blanchard (described on page 9). Robin Huard noticed tremor and unusual body movements among the early signs with Duane when he was a toddler. As he got older, she noticed his arms did not swing when he walked and instead hung at his sides. When he became very ill in his late 20s, his legs jerked and spasmed at night; he began to lose his balance quite often and started falling more frequently. "While shopping with Duane during the holiday season, his brother witnessed him just tip over and fall at an electronics store," Robin said. Although he's doing better since beginning treatment, Duane wrote in during the meeting to say, "The largest obstacle is not being able to walk. Every day is different, but most days are very difficult. It limits my independence every day." Robin indicated that very recently his problems with balance and falling have returned.

For others, problems with balance and mobility appear later and may became more pronounced with age, as has been the case for James Laurie. Wife Shawn said that from the time that James' coordination and balance started to erode at age 19 to his CTX diagnosis at age 32, he developed severe problems walking that didn't resolve with treatment and have become worse in the 20 years since then. "He has fallen many times over the years and one of my biggest worries is that he will fall and injure himself when I'm not home. All our trips outside the home are planned around accessibility," she indicated. Hollisa Rosengrant is spared many of the symptoms others reported, but she too has gait issues. "I haven't fallen and hurt myself, but it's a paranoia I live with."

"Ischemic episodes" is the term Tom Johnson used to describe his wife Debra's experience of aphasia, dizziness, imbalance, weakness, cerebellar tremor, and cognitive decline. Problems with movement were what prompted George Bryce to seek medical attention in his early 30s. Now he's in his early 50s and he's begun using a cane to help steady himself. "I have hyper spasticity. My legs like to jump around at night," George relayed. "I've got real balance issues and I don't know whether that has occurred because of my age or because it is a natural progression of CTX. Just a couple days ago, I was standing there, and I just fell over. I was told when I was diagnosed that CTX affects my spinal cord and my nervous system."

Sangna Odedara was among those who mentioned muscle weakness among her symptoms. Her brother Neel said that growing up, it was hard for him to understand why his older sister was smaller, weaker, and had more difficulty with things than he did. Both of Kay Fischer's sons with CTX, Jacob, age 12, and Herman, age 8, are small in stature and weak compared to their same-age peers by Kay's report.

Two individuals were identified as having difficulty with swallowing and choking while eating, James Laurie and Duane Huard. About five years ago, James gradually lost the ability to swallow food. Wife Shawn stated, "He lost a ton of weight and became very weak, which further limited his mobility. They diagnosed thyroid cancer and he had surgery to remove the thyroid. He still can't swallow very easily and that affects how he is able to take the CDCA medication." Duane's problems began when he started a steep downhill slide in 2016. "He struggled to eat and swallow, and meal times could last hours. Even eating a bowl of oatmeal could take an hour," Robin recalled. He, too, lost a lot of weight, as reported on page 10.

> ***"His bones broke easily and there was a time when every time he fell, which was often, he would break something.***

James Laurie

Bone-related Issues

After receiving the CTX diagnosis, Alex Noa's doctor ordered tests to assess where the unmetabolized cholesterol had accumulated in his body. His mother, Shannon DeLaMar, reported the results of those tests and more recent ones at the meeting, "At age 16 had a bone scan which revealed he had osteoporosis, especially in his right hip. X-rays showed development of a 40-degree curvature of his spine. Three years later, the osteoporosis has increased. His x-rays are stable, but he will need to have x-rays every two years. We are considering spine surgery."

James Laurie also had osteoporosis by the time of his diagnosis in his early 30s. Shawn recalled, "His bones broke easily and there was a time when every time he fell, which was often, he would break something. Now he has learned a way to fall in order to protect himself from breaks."

Avril Dimond's mother, Anne, fell the night before the Unlock CTX meeting. Avril wrote in to say that Anne had broken her femur. It was a complex break and required surgery. Avril also noted that her mother had broken her other femur 15 years earlier, requiring surgery that included implanted plates and screws. "All things considered, she's pretty chippa. She's done this before and she can do this again," Avril wrote from the emergency department of their local hospital in northeast England. *[Editor's note: Anne Dimond passed away in December 2021.]*

Developmental, Neurocognitive, and Communication Deficits

Among the most profound symptoms of CTX are those that affect the ability to learn, think, and communicate. For some individuals, like Eric Stewart, these features appear early and dramatically affect normal development, as described on page 8. Sue provided additional details, "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 just sat on the floor and quietly played with his toys. His IQ was 40 on the Wechsler Intelligence Scale for Children (WISC) scale, the lowest score possible." Now, at age 30, 14 years after being diagnosed with CTX, he lives in a group home for developmentally disabled individuals. Sue continued, "The wheelchair he once required has been given away, but he continues to have a profound expressive language disorder, a severe receptive language disorder, and moderate to severe autism."

Kay Fischer described his sons' limitations, "My older boy, Jacob, is underdeveloped mentally and intellectually, with poor speech and poor learning abilities. Around seven, his tremors started and at

nine he had to be operated on for cataracts on both eyes. Shortly after that, he was diagnosed with autism. Herman was diagnosed with attention deficit disorder around age six. He is also underdeveloped intellectually, but to a much lesser degree than his brother. We have to try to get them both to be social, especially the oldest son who has no friends and is not getting invited to do things after school. To me, that is a great psychological problem, which I think about a lot."

John Wolf said that daughter Ashley's cognitive abilities changed around age six. "Halfway through her first-grade school year, her teacher notified 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 trouble accepting it, but then we came to notice it too. We recognized this might be 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."

Avril Dimond described her mother's cognitive issues this way: "Cognitive delay means difficulty expressing oneself and interpreting what's being asked or expected." Her Aunt Gilly had even more severe social and educational disabilities.

> *"It was becoming difficult to communicate with Duane. His speech became rapid and unclear, and his tongue quivered.*

In addition to the cognitive decline that Duane Huard experienced, his speech changed during that especially rough patch before he was properly diagnosed. Robin described the onset of this issue, "It was becoming difficult to communicate with Duane. His speech became rapid and unclear, and his tongue quivered."

Tom Johnson identified sudden cognitive decline as the most challenging aspect of CTX for his wife Debra. "This is why we felt it was so important to participate. Here you have this brilliant woman, a Rhodes scholar, who has lost mental clarity. Short-term memory was very difficult for her. She had trouble with word-finding and also with word substitution. She had gotten to the point where she really couldn't read a book for not remembering the prior paragraph. She'd ask the kids multiple times a day whether they had done their homework, not remembering she'd already asked. And Debra's biggest fear was, 'At what point am I not really me anymore?'"

Depression, Anxiety, and Other Serious Mental Health Challenges

Depression is one of the symptoms that led to James Laurie getting a CTX diagnosis several years ago, as Shawn described on page 11. She said his mood is "up and down," and he takes antidepressants in an effort to regulate it.

Shannon DeLaMar expressed that her son's mental health issues are her greatest concerns today. "He continues to experience emotional lability, obsessive behaviors, and anxiety. Last week he became obsessed with an issue, and it required me to calmly ask him targeted questions to help him realize he didn't really have an issue." Duane Huard also had compulsive behaviors and increasing anxiety, starting around 2016. Bobbi Blanchard's son Jordan has significant anxiety disorder, obsessive-compulsive disorder, and tics. "These have all contributed to suicidal thoughts requiring medication and continuing therapy," Bobbi stated.

Estefania Amyerich has two older sisters with CTX. Lourdes is now 48 and was diagnosed at age 25; she is the more severely affected of the two. Nuria was diagnosed at 18 and is now 41. They have both experienced mobility issues, spasticity, diarrhea, cataracts, and a lot of neurological issues. Estefania shared, "One of the most despairing effects of CTX for them and for our whole family is that both Lourdes and Nuria have experienced suicidal thoughts and attempts. This seems to be a serious problem that we hear a lot about in our CTX community here in Spain."

Sue Stewart witnessed an abrupt and very troubling change in her son Eric's behavior not long after he was diagnosed and started treatment. "Some of his physical symptoms improved, but the change in his energy levels combined with the 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 to find paid home health workers who could manage him while I was at work, given his rambunctiousness and outbursts," Sue lamented. These changes led to her deciding it was best for Eric to live in a group home for developmentally disabled adults, as described on page 17. He was asked to leave two homes because of his aggressive behaviors before they found the one where he now lives.

Other Symptoms of Concern

Pain – The reports of pain from meeting participants took several different forms, with some referencing the pain associated with gastrointestinal issues, xanthomas, and falls and injuries resulting from balance and mobility issues. At least one person experienced tendonitis and neuropathy; another reported frequent migraine headaches. Finally, a curvature of the spine contributed to chronic pain for one young person.

Seizures – Three individuals mentioned that their family member with CTX experienced seizures.

Fatigue – Ongoing physical and mental fatigue was noted by several participants as an added burden. Some described having "low energy."

Impacts of CTX on Individuals with CTX

Physical Effects

As illustrated through the descriptions of the various symptom clusters in the prior pages, the symptoms of CTX alone and in combination exert a tremendous physical burden, affecting the way the individual feels and functions.

Activities of daily living are compromised for those with moderately severe symptoms, and many are not possible for those at the most severe end of the continuum. Sue Stewart described son Eric's abilities at age 16, just before he was diagnosed, and now at age 30: "At 16, Eric could not bathe or dress himself and he could not brush his own teeth. If we went on an outing of any length, he required a wheelchair. He used an augmentative communication device. Since beginning treatments, Eric has made some improvements, but he remains severely impaired. As his mother and fiercest advocate, I celebrate his small achievements. At the age of 25, Eric learned to get himself a cup of water when he was thirsty. He is now able to dress himself and can buckle his own seatbelt, but he cannot cook for himself or bathe himself. He loves to go to the arcade where he has earned the nickname 'Skee Ball Wizard.'"

Sue Stewart

"Everyday tasks are very challenging for both boys (ages 12 and 8), like personal hygiene and even leisure activities," acknowledged Kay Fischer who participated in the meeting from his home in Norway. "We have to prepare all the meals, lay out their clothing, and help them dress. We practice even simple things over and over again, in hopes that they will catch on. We do our best to teach them things they might be able to do for themselves."

Estefania Amyerich spoke about her eldest sister, Lourdes. "She is the more severely affected of my two sisters with CTX, especially in terms of her neurological 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."

The combination of problems with coordination and movement, weak muscles, and frail bones can lead to a greater risk of injuries, as was heard from Shawn Laurie and Avril Dimond. Constrained physical activity further reduces muscle mass and stamina. Avril and her mother Anne have adopted the mantra, "Use it or lose it," and they work together on physiotherapy, Pilates exercises, and other core and leg strengthening approaches to maintain and preserve as much of Anne's physical function and independence as possible. At age 76, Anne may be one of the oldest living people with CTX. Her sister Gilly died from complications of CTX at age 59 following a lengthy lapse in treatment (described in Section 3 on page 23).

> ***"At 16, Eric could not bathe or dress himself and he could not brush his own teeth.***

Intellectual and Performance Effects

All of the parents who spoke at the meeting referred to struggles in school their children with CTX experienced. Bobbi Blanchard explained that Joelle had done well in first grade, then suddenly couldn't count to 100. They thought it was a phase she was going through, but then things got worse, which ultimately led to her diagnosis. Joelle's slowed cognitive processing and short-term memory problems persisted even after starting treatment. The public school wasn't able to meet her educational needs, so Bobbi teaches her at home now. Her son Jordan has not been affected cognitively in the same way and he's now a senior in high school.

Robin Huard remembers that Duane had some apparent delays in early school years. In sixth grade, teachers raised the issue, but couldn't pinpoint anything. "He didn't put in as much effort on his studies as

Shannon DeLaMar and son Alex Noa

his older brother. By junior high he was falling far behind, so we got tutoring help. English was strong but math was a big challenge. In high school he had trouble with test-taking, but with support, he graduated. He wanted to go to college. After four years, he earned an associate degree from the local community college and got a job at Kroger. He was a good worker there, until his health plummeted, and he had to give up his job," Robin said.

Sangna Odedara had trouble all through school as a child. "My parents were told, 'Some kids just don't like school' while I struggled to keep up," she recalled. "Today I still struggle with certain symptoms like concentration, memory loss, and muscle weakness. But with my family's help, I'm looking for 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."

James Laurie was working full-time in the computer field at the time he was diagnosed with CTX. His mental capacity had diminished some by then, but with treatment he was able to keep pace with work demands even though he never got back to the mental performance level he once had. James wanted to keep working but one day at the office, he took a hard fall down the stairs and broke his arm. He was laid off soon after. Wife Shawn looked for a bright side. "He could be home with our kids while I was at work. I also recognized that meant I would be the sole provider since he was now disabled."

Emotional and Psychological Effects

In 2008, Debra Johnson was president of a manufacturing company with over a hundred employees. "She loved her work and was very, very good at her job," husband Tom declared. Three years later, due to the combined toll of physical and cognitive effects on her health, she was unable to work at all. They moved to a fully handicapped accessible home to accommodate Debra's declining mobility and to enable her to use a power wheelchair in the house. "It was hard for her to lose her sense of self and independence. We resolved to make the best of what time she might have left, to make great memories and basically do everything we could to enjoy every day and with each other and our two children. But Debra is a fighter, and her slogan was, 'Never, never, never give up.' A few months later we got the answer we were looking for – a diagnosis of CTX. Treatment provided improvement of some aspects of CTX and it marked a drastic turning point in our lives. We continue to fight the disease, but we also have a strong sense of hope and optimism that we have the possibility of many remaining years together. Now every day is a 'bonus day,'" Tom exclaimed.

Others shared Debra's feelings of intense distress as abilities were slipping away and during the long, uncertain diagnostic process. The everyday difficulties and diminished quality of life take an emotional toll, too. "There have been times when James has told me he did not want to live any longer due to his physical decline," Shawn Laurie disclosed. "CTX has robbed a lot from James and from our whole family."

Some also spoke to the anxiety of knowing they might pass the disease on to their children. "When my daughter's test came back negative for CTX and as being a carrier, it was a huge relief," said Hollisa Rosengrant. (See bottom of page 19 for additional information about testing of family members.)

Those with noticeable xanthomas, especially on the hand, may find themselves the topic of conversation. Catherine Zonsky shared her experience, "People may know me for a couple years and then suddenly ask, 'What happened to your hand?' I tell them it's a cholesterol deposit that has been there since we met. I recently saw a doctor for another medical issue. When I told him it is due to CTX and what this is, he said, 'I might be able to do something with that.' But I'm leery about such suggestions now that I only have half a tendon on that hand and am concerned about what that might mean for functionality of my hand. I kind of let these kinds of comments go."

The hassles associated with getting appropriate medical care, dealing with insurance companies, and covering out-of-pocket expenses are another source of stress and worry – and sometimes anger – for adults with CTX. The lack of awareness of CTX among primary care providers and limited experience even among specialists creates the need for patients to be vigilant, including those who are not as impaired by the disease.

A major fear conveyed by many of the speakers, patients and family members alike, was the possibility of losing access to their mainstay therapy, CDCA. The emotional burden of this was not to be underestimated, especially among those who had experienced difficulties getting the medication during the time it was coming from outside the U.S. and supply chain or customs issues caused delays. There also

We continue to fight the disease, but we also have a strong sense of hope and optimism that we have the possibility of many remaining years together.

were delays when the manufacture and distribution changed hands from one company to another. "When I had to order my medication from Germany, I asked a friend at church who spoke German to interpret for me," recalled George Bryce. John Wolf remembers well the widespread fear among community members from those times. "I became involved in efforts to maintain patients' access to CDCA when it was only available from Germany, then when we had to work through a pharmacy in London, and later when it became available in the U.S. and went through lots of changes. Those were challenging times that weighed on all of us," he said.

More positive emotions associated with the experience of CTX were the feeling of relief upon diagnosis and finally having a name to put to the puzzling array of symptoms, as was previously stated by Debra above and by Sangna, Catherine, and others. Sangna expressed a sense of gratitude and desire to "pay it forward" for others at the end of her prepared statement, saying, "Without me knowing, CTX held me back from everything. I wanted to do better in school and in life. I am grateful for my family, for the physicians who came up with my diagnosis, and my CDCA treatment. But there is still 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 that I had to. Thank you."

> *"There is still 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 that I had to.*

Impacts of CTX on Families

The toll of CTX is experienced most directly by those diagnosed with it. Yet, Shawn Laurie's statement above, that "CTX has robbed a lot from James and from our whole family," summarizes well the fact that it is also a demanding experience for parents, siblings, children, and others close to the diagnosed individual and the family unit as a whole. Dr. Duell stated in his overview, "When I treat someone with CTX, I really must treat the whole family." The everyday worries and longer-range concerns are evident in many of the quotations throughout this report, as well as in some of the additional statements below.

Personal Impacts

For Narinder Ghara, the stress of carrying a baby that she knew would be born with CTX was overwhelming. (See page 10 for details.) "The news was a big surprise to us. We have a big family here in NY and in India, and no one had ever heard of CTX. We did a lot of searching online to try to understand what to expect. I couldn't enjoy the pregnancy; it was so stressful. But I knew that God always has a plan and maybe what we were going through would give other babies life. It has been that way since Sarabnoor

Testing for CTX Among Relatives of Diagnosed Individuals

Dr. Duell described CTX in technical terms as a "recessive genetic disorder caused by **biallelic mutations in *CYP27A1***, the gene encoding sterol 27-hydroxylase, a cytochrome P450 oxidase." He went on to explain, "What that means is you need to inherit a polymorphism (sometimes referred to as a variant) from both your mom and your dad." As has been stated elsewhere in this section, four meeting participants described how the diagnosis of one family member led to a second diagnosis within their family: Bobbi Blanchard's children Joelle and Jordan; Kay Fischer's two sons; Avril Dimond's mother and aunt; and Estefania Amyerich's two sisters.

Other participants indicated that testing of family members led to important news about their status as carriers – or not: Bobbi Blanchard's third child, Jace, was tested and found not to have CTX and is not a carrier; this was also the case for John Wolf's son, Jacob. Shawn Laurie reported that both her children are carriers, but neither of her two grandchildren have been tested. Hollisa Rosengrant had her daughter tested at age three and was relieved to learn she does not have CTX. Narinder Ghara's positive test as a CTX carrier led to testing by amniocentesis of her unborn son who was determined to have CTX; her older son was tested too and does not have CTX. One of Sue Stewart's other sons was tested for CTX and does not have it; a half-sibling of Eric on his father's side was identified as a carrier.

Herman, Jacob and Kay Fischer

In discussions about this topic with meeting participants, there was a sense that testing of nuclear and extended family members was somewhat sensitive. Some expressed that family believed the risk of being either a CTX carrier or having a dormant case of CTX to be extremely remote. Others said they just didn't want to "go there" with family, even though their own situations were filled with heartbreak. For others, limited access to genetic testing was one more barrier to taking action or encouraging others to act.

was born. There have been so many difficult times, and I don't know whether I'm doing the right thing. They have to draw blood from my little baby – so many tubes, so often. He cries in pain and it's very stressful. I want to do what's best for him. What I've heard today is everybody goes through a lot of pain. A lot of pain. In some ways, I feel like the luckiest person in the room. Nobody knows about CTX, so it's pain we bear on our own," she acknowledged.

> ***My biggest problem is that I have to accept that the boys will probably have to have this level of help for the rest of their lives.***

Kay Fischer revealed how deeply his two sons' journeys with CTX had affected himself and their mother. "The situation as a whole has become very difficult for family life and for us as parents. Their mom and I have become a team of nurses and psychologists and social workers. We are activators (advocates) for the boys and have had to become specialists for children with special needs, just to get them the services they are rightfully entitled to. Lots of time and energy goes to that. So, life has become about managing and taking care of the boys, rather than doing typical married life activities or being a loving couple. We both became depressed, and we both had to seek a counselor's help to be able to deal with the situation. That ultimately led to divorce. My biggest problem is that I have to accept that the boys will probably have to have this level of help for the rest of their lives. They might not be able to live an independent and fulfilling life, which is every parent's dream when you hold your little baby in your arms. We are trying our best, teaching them everyday things like showering, brushing their teeth, but we don't really know what we can expect." Kay's words strongly resonated with other parents.

"Like Kay, I am also divorced and went through lots of therapy. I ended up being a single father of two teenage kids, one with CTX, and that was difficult. I just want to highlight that as something that is really an extension of caring for a young individual with CTX," John Wolf added by phone following Kay's remarks.

Shannon DeLaMar expressed a similar concern about the future for her son. "I'm happy to report that 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. I worry about who's going to help him work through the day-to-day struggles when I'm no longer living. I guess I will have to trust in God. We are so happy to see CTX get this attention today. I hope this information contributes to a better understanding of CTX and how it affects lives, not just the patients' lives but the families' lives, too."

Sue Stewart with son Eric

Bobbi Blanchard also raised the worry about how her children will manage. "We have considerable fears about how the kids will handle these things in adulthood without us. Will they continue therapies and treatment as prescribed without their parents nagging them? If they stopped treatments, how quickly will they decline and will they even know that they need to get back on track? 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's 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-late."

Another fear that family members experience is for the very life of the person with CTX, especially before a diagnosis is known. These quotes have appeared earlier, but they are repeated here to emphasize the psychological weight of these worries.

> *"At age 16, Eric was very ill. I feared he was dying." – Sue Stewart*
>
> *"Duane looked like a zombie. He was so ill. We were frightened for him and thought he was dying." – Robin Huard*
>
> *"The trend of Debra's symptoms and her function were both in steep decline. Just speaking between ourselves, we felt that she would be lucky to see the age of 45." – Tom Johnson*

Family Functioning

"As a family, we have had to completely adjust our entire lives to take care of Duane," stated Robin Huard plainly. Sue Stewart also noted, "Eric's CTX has greatly impacted our family, including his two older half-brothers."

The impact on sibling relationships was another topic that Kay Fischer described in detail. "My younger son, Herman, is very affected by his older brother's behavior and challenges. He doesn't really have a 'normal' place in the family as a younger brother or son should have. It's difficult for him to understand why Jacob is the way he is. He has to deal with other kids commenting on his brother's odd behavior in school. He

probably feels he isn't seen as much as he should be seen by us and that he has to stand behind the greater needs of Jacob. That seems unfair to him, and it is a source of conflict between the two boys," he reported.

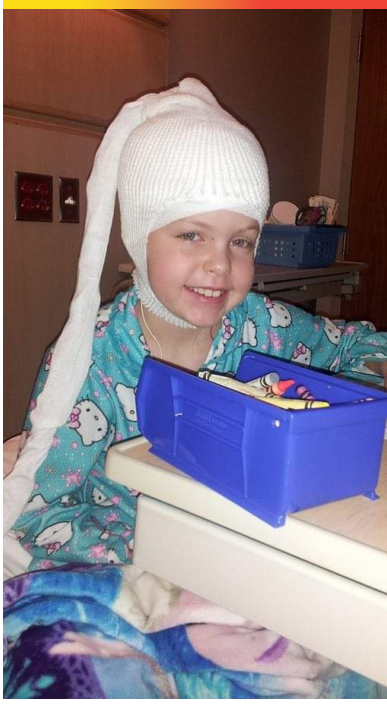
Shannon DeLaMar said Alex's siblings sometimes doubted what was happening. "One sibling said, 'I think he is faking' and I would ask, 'Could he fake having osteoporosis in his right hand [as a kid]? Could he fake the findings on his MRI?' Now they understand. I can relate, Kay." Neel Odedara responded too, "That is an experience I can relate to in our family. My sister, Sangna, is the middle sister and there were challenges navigating the differences between siblings as a result of the condition, especially in childhood when you don't fully understand and appreciate what's going on."

John Wolf added his experience, as well. "I was not aware, or maybe was oblivious to it because we were so focused on Ashley's treatment and condition, that my son felt like he was in second class in our family. He expressed that to me later."

For Avril Dimond, CTX has affected the way she's lived her entire adult life. "My father died when I was 17 years old, and I became Mum's carer. She has managed to continue living in her own home with help from aides. I live nearby, and we are dedicated to meeting each new challenge as it comes along, and there are many. I will become Mum's 24/7 carer when she needs me, but I've got to enable her to do the simple, everyday things we take for granted for herself as long as she can," Avril stated with conviction.

Describing husband James' difficulties with mobility and falls, Shawn Laurie noted a way in which that experience shaped her son's life. "One time, our 16-year-old son had to take James to the emergency room 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."

Another observation that Neel Odedara made as he listened to community members' experiences was, "how family members try to navigate what it means to have a 'normal life' and to be able to achieve that. There are differences in progression of symptoms that make it difficult to predict and anticipate what that means for the affected family member and the family as a whole." Uncertainty was a prevailing theme that arose over and over again throughout the meeting. There was vast uncertainty during the diagnostic journey, and uncertainty took different forms once a diagnosis was found and treatment began.



Joelle Blanchard

Financial Impacts

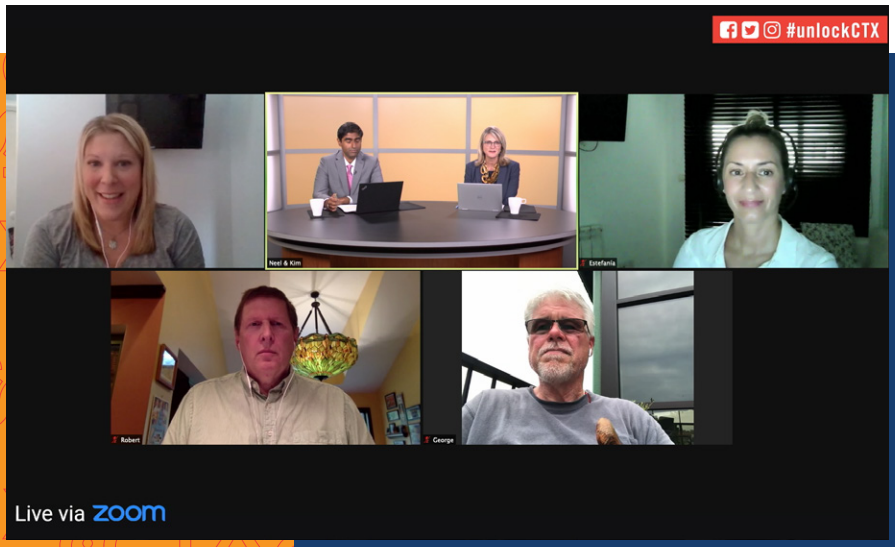
As some of the statements quoted in prior passages indicate, CTX causes substantial financial burdens and challenges that also amplify some of the personal and emotional effects on families.

"During Eric's diagnostic journey, I sought the advice of many practitioners and Eric participated in a great many therapies. This was a great burden in terms of financial expense and time for our family. I was a single parent, so all this was on my shoulders, and I needed to continue working to support all four of us. Today, Eric 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," Sue Stewart noted with resignation.

Bobbi Blanchard expressed similar circumstances and concerns. "Even on our comparatively short diagnostic journey, 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. Right now, both kids are on my husband Tim's insurance, which we've been incredibly grateful for. During the diagnostic journey, we were able to see a lot of specialists that we couldn't have afforded to see otherwise. During COVID, Tim was laid off and we had great concern that the kids wouldn't be able to see the specialists they need to see. At some point when they are off Tim's insurance, chances are, with some of the physical and cognitive difficulties they experience, they may not have the kinds of jobs that provide the insurance coverage they need. So, we worry not only about medication, but access to specialists as well."

> "
>
> ***The helplessness of watching your daughter deteriorate and your medical debt rapidly increase is something we're still recovering from today.***

The worry about continued insurance coverage was one Shawn Laurie identified, too. "When James stopped working, I became the sole provider for the family. At that time, the cost of the medicine was our biggest concern. My job provides health insurance, and so far, our insurer has covered the medication, but we live with fear that the coverage might end because CDCA is not FDA-approved for CTX. I also worry what would happen if I lost my job."



SECTION 3:

CURRENT AND FUTURE APPROACHES TO TREATMENT

> ***If untreated, CTX can be a progressive, debilitating neurologic condition. It can lead to xanthomas on the tendons and in the brain. In the untreated state, osteoporosis and atherosclerosis can occur. I can't emphasize it enough that early diagnosis and treatment is essential.***
>
> *– Dr. Duell*

Therapies Used to Treat CTX

In presenting the clinical overview of CTX at the beginning of the meeting, Dr. Duell identified chenodeoxycholic acid (CDCA, marketed in the U.S. under the name Chenodal) as the standard of care for CTX. CDCA is a primary bile acid that is deficient in individuals with CTX. It is administered orally; adults typically take three doses of 250 mg each day. Dosing for children is based on body weight.

Shawn Laurie

Dr. Duell also addressed how CDCA is currently prescribed to children and adults diagnosed with CTX. "CDCA is an FDA-approved drug, but it is approved for the dissolution of gallstones. It is actually not used that much for gallstones; the primary use of CDCA is for CTX. When we use CDCA for treatment of CTX, technically it's an 'off-label' use. Cholic 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. Ultimately, the hope is to have the FDA approve [CDCA] for CTX because it is the recognized standard of care worldwide," he stated.

Dr. Duell outlined additional therapies used to manage complications of CTX, discussed in this section through the experience of patients and caregivers. He also recommended that individuals with CTX follow general preventive health recommendations for "heart-healthy" dietary habits, regular physical activity, and abstinence from smoking. Finally, he emphasized the connection between early, consistent treatment and health outcomes. "If untreated, CTX can be a progressive, debilitating neurologic condition. It can lead to xanthomas on the tendons and in the brain. In the untreated state, osteoporosis and atherosclerosis can occur. I can't emphasize it enough that early diagnosis and treatment is essential."

Prescription Medications

CDCA – All of the patients participating or represented by participants in the Unlock CTX meeting were currently being treated with CDCA, affirming Dr. Duell's description of it as the standard element of care. For most, treatment with CDCA began within weeks or months of diagnosis. For some, there was a lag in accessing the treatment initially or difficulty maintaining access due to a variety of issues, some of which stem from it being prescribed as an off-label therapy or not being available from a U.S.-based manufacturer in years past (see pages 18-19).

Individuals described seeing benefits upon starting CDCA therapy. John Wolf recounted Ashley's response, "Over the course of the first year, her 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. The results for electrical activity shown on her EEG were much improved compared to the EEG done before treatment started," he said. "Today Ashley is 20. She lives independently, works, drives, and has a three-year-old child. Without her diagnosis at age 10 and treatment, I'm afraid I would be telling a very different story."

Robin Huard reported similar observations, "To the disbelief of Duane's doctors, we could see very subtle changes within the first two weeks of treatment with CDCA. Within six months, 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. He began gaining weight, eventually reaching his current weight of 163 pounds from a low of 102 pounds. He can absorb nutrients now." While Duane continues having difficulties, Robin said, "We are thankful to have determined the underlying cause of many of these problems as CTX and to have CDCA 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."

"Within a couple months of diagnosis, Debra started treatment," stated Tom Johnson. "Over the course of the next year, she improved. Some of the cognitive symptoms improved somewhat and seemed to stabilize, in that they weren't progressing as rapidly. Her cerebellar tremor seemed to get better, which helped with her mobility. Importantly, she could read a book again. She felt like she had her life back, or at least life wasn't getting worse from a functional perspective."

Bobbi Blanchard also noted that the progression of CTX for both her children slowed once they started treatment with CDCA. Joelle's tremor and coordination improved; treatment also seemed to prevent Jordan from experiencing cognitive decline. Shannon DeLaMar said that her son's neuropsychiatric symptoms improved a bit and the white matter deposits that were detected by MRI have not changed since his treatment began three years ago.

As Shawn Laurie noted, improvements were lost if access to CDCA was interrupted. "James has been on CDCA for 23 years – actually on and off, due to challenges getting the medication at different points in time. When James started on CDCA, 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' gait, his mental acuity, and his affect improved as well. When he had to go without the 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."

Avril Dimond shared the wrenching story of the decline that her mother and aunt experienced when the UK's National Health Service instituted a cost-saving measure. They substituted ursodeoxycholic acid (UDCA, a different bile acid used to treat gallstones) for CDCA. "I realized this substitution could be wrong, but when I began questioning, I was rebuffed. I reached out to Dr. Gerald Salen, and he answered my email with the unequivocal statement that UDCA was 'an ineffective treatment' for CTX. I used his email in my repeated appeals with the authorities, medical professionals, and the pharmacies. This fight went on at least 18 months from the time I realized the medication had been changed. Aunt Gilly may have been on UDCA even longer than my mum." Over this time, both women declined. Avril continued, "Aunt Gilly lost her ability to talk, to walk, and developed a swollen belly like a third-world malnourished child. She had problems swallowing and drooling and had to use a feeding tube. She had an increasing number of seizures and falls and had to use a wheelchair full time. She was no longer able to bear weight nor stand, and she could not hold herself upright without trunk support. She developed gallbladder problems and sepsis and died at age 59 before I was able to get her back on CDCA treatment. My mother regressed as well, but fortunately Dr. Salen's email helped me win the appeal and I got her back on the correct medication in time to save her life. Mum is now 76 years old."

Margaret Dennett shared her daughter's treatment story via written comment. "When her condition was diagnosed at age 27, Dominique was given UCDA for the next 14 years. I noticed her condition was deteriorating so I corresponded with the United Leukodystrophy Foundation and was informed that she should be taking CDCA instead. Since then, we changed specialists, and Dominique started taking CDCA."

Antidepressants and anti-anxiety medications – In response to a polling question about medication use, antidepressants ranked second after CDCA, and anti-anxiety medications ranked third among those responding. It can be challenging to find medications that are effective, as Robin Huard testified. "It took well over a year [after starting on CDCA treatment] for doctors to find the right balance of medications to enable Duane to conquer his anxiety and compulsions."

Medications Given to Address CTX Symptoms Prior to Diagnosis

The lengthy diagnostic process – including frequent misdiagnoses – often results in physicians prescribing medications that might relieve suffering or improve function. This list includes medications participants mentioned taking prior to getting diagnosed with CTX.

Allergy medications

CellCept

Corticosteriods (oral and intravenous)

Imuran

Intravenous immunoglobulin (IVIG)

Loperamide

Rituxan

Use of CDCA During Pregnancy

Two participants had experience to relay regarding treatment with CDCA while pregnant – John Wolf, through the experience of his daughter, and Hollisa Rosengrant. Although there have been no formal studies conducted, both were advised by CTX experts that based on clinical experience, the risks of non-treatment during pregnancy appeared to outweigh the potential risks of treatment.

Hollisa described pregnancy as the most stressful period of living with CTX. "There wasn't much evidence to go on. I was referred to a maternal and fetal medicine specialist who told me to stop treatment right away. But he was reacting to the black box warning about CDCA treatment of gallstones during pregnancy, not CTX. I consulted Dr. Salen and Dr. Duell who both agreed I should continue treatment. At my request, they contacted my OB care team and reached agreement. It added anxiety to an already high-risk pregnancy. When my daughter was born, the delivery nurse told me she couldn't give me my medication because of the warning labels flagged by the hospital pharmacy. I feared this might happen and had put the medicine in my overnight bag so I could continue my treatment."

Muscle relaxants and pain relievers – As the table on page 9 reflects, participants represented a full spectrum of age of diagnosed individuals. Those at the older end of the continuum were more likely to be treated with medication for pain and muscle problems including clonus and spasticity. George Bryce indicated that he uses a Baclofen pump to address the hyper-spasticity in his legs. James Laurie also used a Baclofen pump, according to his wife, Shawn.

Other medications – Individuals with CTX rely on other medicines to address osteoporosis and cardiovascular abnormalities, provide symptomatic relief, and address comorbid conditions. Estefania Amyerich's older sister experienced a significant decline, even with CDCA treatment. "The severity of Lourdes' condition caused us to look into more experimental treatments. Based on a report published in 1993 by researchers 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 not covered by our public health system and was very expensive. It also was not available locally, so we had to travel frequently and spend long hours in the infusion center. In spite of some signs of neurological improvement, the benefit did not justify the cost and hardship of the treatment. We made the decision to discontinue plasmapheresis after 12 sessions," Estefania stated.

Surgical Treatments

Cataract and Vision-Related Surgery – Numerous participants described the early onset of cataracts in one or both eyes and surgical treatment required. (See page 13.) As described earlier, several individuals required more than one surgery to address complications in the initial surgery or to treat subsequent vision-related issues that developed.

Removal of Xanthoma(s) – Catherine Zonsky and Hollisa Rosengrant each reported that the appearance of unusual growths on their hands led them to consult surgeons. Catherine's description of the events leading up to and following that surgery are described on page 14. When the growth returned some years later, rather than have a second surgery she consulted additional specialists that ultimately led to the diagnosis of CTX. Hollisa's surgeon questioned the nature of the growth and referred her for further testing that led to the diagnosis of CTX. Margaret Dennett wrote that her daughter Dominique had surgery at age 25 to excise the lesion on her left Achilles and to reconstruct that tendon.

Other Surgeries – Two individuals reported requiring attention as a result of injuries that may have been related to mobility issues due to CTX. Duane Huard shattered his kneecap when he took a hard fall at work. Duane also required surgery to remove part of a Desmoid tumor on the ball of his foot. Anne Dimond required orthopedic surgery and implantation of metal plates and screws following two separate falls; the second one occurred on the night before the Unlock CTX meeting.

Shannon DeLaMar indicated that she and her son were considering spinal surgery as a means to correct the severe curvature of his spine. As the years coping with CTX went on, James Laurie experienced tremendous difficulty with swallowing and eventually underwent a cricopharyngeal myotomy to ease (but not fully resolve) this problem. James also had his thyroid surgically removed after developing thyroid cancer, the relationship of which to CTX remains unclear. Sue Stewart's son Eric had hernia repair surgery; again, the relationship of this condition to CTX is unclear.

Supportive Therapies

Participants referenced a wide array of approaches to improve function and well-being both before and after diagnosis with CTX. The most frequently cited were physical therapy, occupational therapy, and speech therapy – alone or in combination with one another. Chiropractic care was another approach used to improve physical functioning. Avril Dimond emphatically endorsed the benefits her mother receives from physiotherapy, including Pilates exercises and core training. "This routine is helping her retain as much function as possible for as long as possible. It has been hard to continue physio during COVID and to find private therapists willing to work with her during the pandemic."

Avril also wrote in to share how important diet is to her mother's health. "We use digestive enzymes, probiotics, and a careful diet in an effort to maintain good gut health." She felt that malnutrition earlier in her mother's life had contributed to increased severity of osteoporosis that led to serious fractures.

Several people reported on the need to use assistive devices, especially to help with mobility. Shawn Laurie's video included a segment showing her seated on the tailgate of their specially equipped van.

She was surrounded by walkers used inside and outside their home and a scooter used by James outside their home, depending on the nature of the activity and distance he might have to traverse.

Duane Huard experienced difficulties with sleep that were identified as being related to sleep apnea. It took considerable trial with various continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP) machines before they found that an adaptive servo ventilation device provided the best airway support to enable sleep.

At the time of the meeting, the Johnsons had just welcomed a service dog, Storm, to their family. "He's an amazing dog and we're glad to have him join the family. It has been a bright spot," beamed Tom. Storm was placed with them and they trained to work with him through Canine Companions for Independence.

Debra Johnson with her Service Dog, Storm

Downsides and Burdens of Current Treatments

CDCA

There is no question that meeting participants relied heavily on and were extremely grateful for the benefits of CDCA treatment. They did, however, identify treatment-related downsides and burdens.

Downsides – At least two individuals, Eric Stewart and Duane Huard, experienced an exacerbation of neuropsychiatric symptoms that appears to have coincided with starting CDCA therapy, as described by Sue Stewart on page 17. Robin Huard reported a similar experience. She stated, "The CDCA awakened Duane's body. The new sensations he was feeling, including pain, completely overwhelmed him and crippled him. His anxiety and obsessive-compulsive symptoms went into overdrive and began to completely take over his life and our lives." She mentioned that Duane currently takes eight medications a day to manage CTX and these complications.

Some of the individuals with longer term experience with CDCA suggested that it seems to them that it loses effectiveness over time. Shawn Laurie said this at the end of her prepared statement, "James is now 55 and we may have reached the limits of what CDCA can do for him." Joe Shore, age 35, sent this written comment during the meeting: "I don't feel like the medication is working at times. I have been getting a lot worse over time." His mother also commented in writing with these details, "He needs help with the xanthomas that are getting bigger on his heels and legs. Also his eyesight and his teeth are deteriorating." George Bryce also questioned whether the increased difficulty he is currently experiencing with balance and mobility is due to age or a waning effect of the medication benefits.

Burdens – The formulation of CDCA presents several challenges. Parents of growing children indicated that getting the dosage right requires constant calibration because it is based on body weight. For Narinder Ghara's newborn son, there was little experience to go by in terms of when to start treatment, dosing, and the best way to get the baby to take the treatment. (See page 10.) Kay Fisher mentioned that keeping up with his sons' medication management is challenging. "We are making the mixture ourselves every four days and giving it to each of the boys three times a day. It spoils quickly, and it's sensitive to changes in temperature which is quite hard in the Norwegian climate with its extreme highs and lows." Parents of teenage patients noted that having to remind their sons and/or daughters to take their medication multiple times a day was a source of tension and worry. It reinforced fears about what might happen if they weren't there to ensure their child took his or her medication. Bobbi Blanchard spoke about the tricky transition for her daughter. "The frequency of dosing is the hardest thing for Joelle. We set lots of alarms, especially because Joelle has short term memory issues. She makes a hash mark near the pill bottle to help her keep track of each dose as she takes it."

For others who experienced difficulty swallowing, the pill form was hard to ingest. Shawn Laurie said this was the case for James, and she knew that he didn't always take the medication as often as he should because it is physically hard for him. "I know this isn't ideal, in terms of him getting the full benefit," she admitted. The consequences of interrupted (or non-adherent) therapy carried an emotional burden for those who had experienced this once or more.

One of the greatest burdens associated with CDCA treatment is related to the challenge and cost of accessing it, as discussed on pages 18-19 and 21. Several of the participants representing long-term

> ***"There is no question that meeting participants relied heavily on and were extremely grateful for the benefits of CDCA treatment.***

Herman Fischer

Jacob Fischer

> ***My biggest problem is to deal with the fact that all my dreams and hopes for our children's lives and futures are crushed.***

experience referenced the years during which CDCA was not available in the U.S. and had to be obtained from Germany and then England. During this time there were frequent problems with shipping and customs that could delay receipt. Others brought up the access challenges created by CDCA not being FDA-approved for CTX and therefore often contested by insurance providers. Bobbi Blanchard spoke to this, "Once Joelle and Jordan were diagnosed, it took three months to start treatment. The vast majority of that time was spent convincing the insurance company to approve an off-label medication." Neel Odedara added this experience, "Personally, I have a minor panic attack whenever I get a call from my sister's insurance company. The sheer uncertainty around the continued coverage is an additional burden on families."

Sue Stewart shared a frightening event that put her son's treatment in jeopardy. "Because Eric is so severely disabled, he is covered by Medicare and Medicaid. His Medicare Part D (for medications) is covered by the state of Oregon. About five years ago, the Medicare Part D provider he had then took CDCA off its 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 a very frightening situation, and 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. We came very close to the cut-off date before Eric's Medicare Part D was changed. The fact that CDCA coverage is left to the whims of Medicare Part D providers is very frightening to family members."

Other Treatment Burdens

Other burdens that were identified by participants included the need for regular monitoring via laboratory tests and imaging by MRI. Coordinating all the medical appointments and specialists involved in the treatment of CTX is time-consuming and the level of care required imposes financial burdens on families, as described on page 21.

Treatment Outcomes Desired and Unmet Needs

Among the most often-mentioned gaps in treatment was that while CDCA slows or stops progression, it does not completely reverse deterioration that occurs before treatment starts (or that occurs if treatment is interrupted), as illustrated through statements in earlier sections. Participants articulated a strong desire for therapeutic approaches to restore lost function.

Additionally, participants' experience with CDCA indicated that it leads to more immediate improvement of certain symptoms – gastrointestinal symptoms, nutrient absorption and weight gain, tremor, and fatigue – compared to others. CDCA seemed to have a limited effect on cognition, and this was a definite need identified by participants. They also stated needs for therapies to address mobility, balance, coordination, and neuropsychiatric symptoms. There were insufficient means of addressing osteoporosis and bone-related issues, including fractures and spinal curvature. Problems swallowing have a direct impact on nutrition and medication adherence, yet there are few means available to effectively address them. The

parents of children whose CTX presented with autism-like behaviors, expressed great unmet need and desire for therapies to address this complex.

> *"I wish there were more treatments that could lead to improvements in James' quality of life, especially his mobility, his mood, his ability to work, eat, and play without so many limitations." – Shawn Laurie*

> *"There is a lot more that can be done to help CTX patients maintain strength and gut health and vitality. More attention is needed to address the damage to the brain which wouldn't happen if there were earlier and more constant treatment." – Avril Dimond*

> *"We need more treatments that are effective in taming the neurological problems and psychiatric symptoms." – Estefania Amyerich*

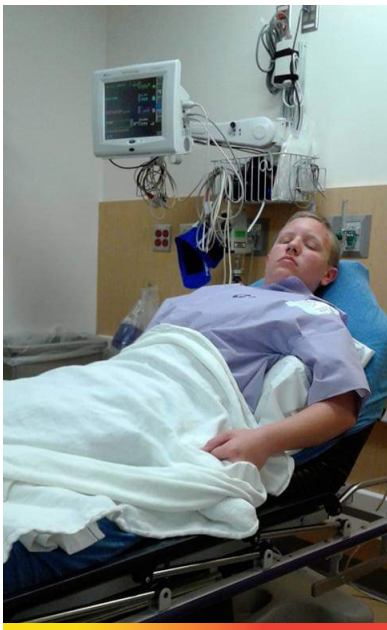
> *"My biggest problem is to deal with the fact that all my dreams and hopes for our children's lives and futures are crushed. Especially my oldest son [who has the autistic features] will need help for the rest of his life. He is not going to be able to read and do simple math problems which limit his chances for an 'independent and fulfilling' life. This is very hard to accept and to deal with." – Kay Fischer*

> *"We need to find a medication that stops CTX from progressing. This is an urgent priority. We need help with the side effects, including problems with eating, problems with speaking, and kidney stones that form every six months." – Alicja, caregiver writing from Massachusetts*

> *"We have little knowledge of what to expect for the future of our two adult children living with CTX. We don't know how to plan for their needs after we are gone." – Mary Beth and Mario, parents writing from Washington*

"

We have little knowledge of what to expect for the future of our two adult children living with CTX. We don't know how to plan for their needs after we are gone.



Jordan Blanchard

Another unmet need is for more evidence to guide use of current treatments in certain circumstances, like pregnancy. (See sidebar, page 24.) As early detection becomes more common, there will be an even greater need to understand when to begin CDCA treatment and how to administer it, as Dr. Larson stated (see page 12). Formulations for pediatric use and longer-acting forms would reduce patient and caregiver burdens, including some of the current uncertainty involved in dosing growing children based only on body weight. Formal guidance for long-term use, including dosing strategies to maintain treatment benefits in later years, is another unmet need. Written comments from Maria, mother of a recently diagnosed seven-year-old with CTX, summed up these challenges. "I'd like to know of other cases of diagnosis at this age and their evolution with current treatments. Additionally, I'd like to further understand the long-term impact of CDCA, including if and how treatment needs to be adjusted with variation and progression in symptoms. These are all key uncertainties we're hearing about."

Ongoing mental health support is needed for patients and family members, as Neel Odedara pointed out. "The challenge of navigating the symptoms and dynamics within the family underscores the critical importance of mental health support. It is often unappreciated and is something that must be maintained after the diagnosis," he said. Avril Dimond and others highlighted the need for more attention to understand how to make better use of dietary and physiotherapy supports to preserve and enhance function.

Individuals also called for curative treatments that address the underlying defect that leads to CTX. "I operate a small organization to connect people living with CTX in Spain, comprising about 20 families. Like my sisters, I hear other community members speak about the need for more treatments, especially ones to address the root cause. Gene therapy is our hope," Estefania Amyerich testified. Shawn Laurie expressed a similar hope, "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 low-density lipoprotein (LDL) apheresis. Both our children carry one recessive copy of the gene that causes CTX. Our two grandchildren have not been tested. I hope 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."

Newborn screening was an unmet need mentioned by nearly every participant. Another research need raised is to gain a better understanding of what appear to be different subtypes of CTX, based on when symptoms first appear, which ones present first, and the rate of symptom progression. Dr. Kumar of the

FDA pointed to the need for more studies of the natural history of CTX and patient registries to better document patient experience over time.

Dr. **Robert Steiner,** a physician and professor at the University of Wisconsin who encountered his first CTX patient in 1997, spoke to the need for more formal medical education. "There is little awareness in the medical community about CTX. This leads to delayed diagnosis and the extended diagnostic odysseys we've heard about from so many of today's speakers. This in turn means some patients will have already suffered significant complications that are challenging to address. Earlier diagnosis could come with newborn screening and also with adding the CTX gene to multi-gene diagnostic testing panels." He continued, "There are too few experts in CTX to manage the patients or even to be available to answer questions from healthcare providers with little experience with CTX who find themselves caring for a person with CTX." These comments also connected to other participants' statements about opportunities for earlier diagnosis and treatment that could be addressed by better education of physicians, especially optometrists and ophthalmologists who could refer patients with early onset cataracts for genetic evaluation and testing and potentially accelerate diagnosis and care. (See page 10.)

Ashley and John Wolf with granddaughter

Connected to the topic of the need for more medical education is the contributing factor that CDCA is prescribed off-label for CTX and therefore physicians may not recognize CTX as a treatable disease. As described in earlier sections, this also contributes to access issues for diagnosed patients, compounding other unmet needs, especially in circumstances where treatment is interrupted due to lack of coverage. Several participants' experiences emphasized the need for more education about how to effectively navigate coverage issues and the types of evidence that can be useful in appeals.

A final unmet need expressed by participants is for long-term support services, including residential services, for dependent patients as they – and their parents and family caregivers – age. This need was especially acute for some participants facing the prospect of no longer being able to provide the level of care their loved one requires.

In Conclusion

The Unlock CTX meeting provided a unique venue for members of the global CTX community to describe their experiences and articulate their needs and expectations. Their powerful statements documented the burdens the disease imposes on patients and family caregivers and outlined a research, education, and policy agenda worthy of shared commitment. ULF President, Robert Rauner, commended all the participants in his closing remarks. "This has been a very enlightening meeting. I've met many of you over the years, so it's heart-wrenching to hear the stories that you shared. I know it takes a lot of courage to come to a meeting like this and bare your soul. You have done a great job communicating the challenges that CTX entails. I hope that the FDA staff and other people attending learn a lot from today's meeting."

> ***"It's heart-wrenching to hear the stories that you shared. I know it takes a lot of courage to come to a meeting like this and bare your soul. You have done a great job communicating the challenges that CTX entails.***
>
> ***– Robert Rauner, President of United Leukodystrophy Foundation***

ACKNOWLEDGEMENTS

The United Leukodystrophy Foundation expresses gratitude to the following individuals who have enhanced the Unlock CTX PFDD Initiative:

All members of the CTX community who participated in the meeting through recorded presentations, live on-camera remarks, comments provided by telephone, and written comments submitted before, during and after the meeting.

John Dudley, **Eric Quigley**, and **Kyle Rhoderick** of Dudley Digital Works for creative and technical services to broadcast the PFDD meeting live and preserve it for later on-demand viewing.

William Lewallen of the FDA's Office of Strategic Initiatives, Center for Drug Evaluation and Research for providing counsel and encouragement throughout the entire process of meeting planning and follow-up.

Keely Mata and **Christopher Rice** of the United Leukodystrophy Foundation for support with initiative outreach, planning, communications, and editorial review of this report.

Samantha Mayberry of the Kith Collective for content development, meeting planning, meeting and report preparation, communications for the initiative, and interacting with community members calling in during the Unlock CTX meeting.

Kim McCleary of the Kith Collective for initiative strategy, content development, speaker preparation, meeting moderation, and principal authorship of this report.

Neel Odedara of the CTX Alliance for support with content development and co-facilitation of the Unlock CTX meeting.

Jean Pickford of Pickpoint LLC for assistance connecting with founding members of the CTX Alliance and additional meeting support.

Julie Rathjens of Hello Brand for design of the Unlock CTX logo and production of other creative materials, including this report.

Robert Rauner of the United Leukodystrophy Foundation for initiating this project on behalf of the CTX community, guiding its successful execution, and seeing it through to fruition.

Members of the CTX Alliance Board of Directors for support of initiative strategy, meeting content development, and review of this report.

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Thank you to these generous sponsors for their unrestricted educational grants in support of the Unlock CTX initiative:

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With appreciation for the partnership of these organizations who helped to engage members of the CTX and leukodystrophy communities in the Unlock CTX initiative:

Alex The Leukodystrophy Charity – Helping to Cope – Helping to Hope

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Leukodystrophy Resource Research Org Inc

AEXCT Spain
ASOCIACION ESPAÑOLA DE XANTOMATOSIS CEREBROTENDINOSA (AEXCT)

BIOGRAPHICAL INFORMATION FOR MEETING MODERATORS AND SPEAKERS

Robert Rauner (Introductory and Closing Remarks)
President, United Leukodystrophy Foundation

Robert Rauner is the parent of a son, Kevin, who passed away from adrenoleukodystrophy (ALD). His son Paul has adrenomyeloneuropathy (AMN). Mr. Rauner has been involved with the ULF since 1994 and has been a Board Member since 2000. He has served as Treasurer of the ULF and now serves as President. He is a retired UPS truck driver and is now devoting his retirement to the future of the ULF. His hope for the future is to help researchers find treatments and cures for leukodystrophies, as well as to support affected families. His hobbies include golf and fishing.

K. Kimberly McCleary (Moderator)
Founder & CEO, Kith Collective

Kim McCleary has been at the forefront of patient engagement for 30 years. She is a nationally regarded subject matter expert on patient-focused medical product development, patient-centered benefit-risk assessment, and organizational change. Ms. McCleary has authored scores of publications, served on dozens of steering committees and advisory boards, is a sought-after speaker, and has an extensive network of leadership contacts. Her passion for this work is rooted in personal experience, lived and as a family caregiver.

Ms. McCleary founded the Kith Collective in 2018 to speed adoption of patient-centricity by life science companies, not-for-profit organizations, and academic research teams. She has been involved in numerous patient-focused drug development meetings, including sessions led by the FDA and by patient advocacy organizations. Ms. McCleary lives in Arlington, Virginia and is a graduate of the University of North Carolina.

Neel Odedara (Moderator)
Secretary of the Board of Directors, CTX Alliance

Neel is an Associate Principal with Trinity Life Sciences and has over 10 years of experience advising small to large global biopharmaceutical clients across a wide range of therapeutic areas including rare/orphan diseases, neurology, and cardiometabolic conditions. Neel's experience spans multiple functions within the life sciences including commercial assessment, new product planning, brand/commercial strategy, launch, access, and patient engagement. Neel graduated from Brown University in 2009 with a B.A. in International Relations.

Neel's journey with CTX began in 2018 when his older sister Sangna was diagnosed at the age of 34 following genetic testing at National Institutes of Health. This followed decades of missed symptoms and misdiagnoses across various physicians and health institutions. For Neel and his family, this experience has ignited a commitment to supporting awareness, advocacy, and engagement on behalf of CTX patients.

P. Barton Duell, M.D. (Clinical Overview)
Knight Cardiovascular Institute and Division of Endocrinology, Diabetes and Clinical Nutrition
Oregon Health & Science University

Dr. Barton Duell has cared for patients with CTX for more than 25 years. Dr. Duell is currently a Professor of Medicine in the Center for Preventative Cardiology at the Oregon Health and Science University. Additionally, he serves as the director of the Lipid-Atherosclerosis Laboratory and Sterols Analysis Laboratory. He is also the director of the LDL Apheresis Unit.

He has served as a clinician. attending physician, and researcher at the Oregon Health and Science University for over 29 years. His other roles include associate editor of the Journal of Clinical Lipidology, editor of the American Journal of Preventive Cardiology, chair of the Clinical Lipidology Committee for the American Heart Association, member of the Board of Directors for the National Lipid Association and American Board of clinical Lipidology, on the publications committee for the FH Foundation, among others.

Dr. Duell attended medical school at the Oregon Health and Science University and did his internship and residency in internal medicine at the University of Chicago and the Oregon Health and Science University. He did a fellowship in Metabolism, Endocrinology, and Nutrition at the University of Washington. He currently resides in Portland, Oregon.

Vijay Kumar, M.D. (FDA Perspectives on Patient-Focused Drug Development and Meeting Testimony)
Center for Biologics Evaluation and Research
US Food and Drug Administration

Dr. Vijay Kumar is a nephrologist and currently serves as a Medical Officer in the Office of Tissue and Advanced Therapeutics (OTAT) at Center for Biologics Evaluation and Research (CBER) within FDA. OTAT regulates new cell, tissue and gene therapies, many of which are targeted to the treatment of rare diseases.

Prior to joining the agency, Dr. Kumar was engaged in the practice of nephrology for over two decades. He completed his medical degree in India. Subsequently, he completed his internal medicine residency at Wayne State University in Michigan and his nephrology fellowship at University of Texas -Southwestern School of Medicine. He is board certified in nephrology and maintains an active physician license in the state of Maryland.

Neel Odedara, Samantha Mayberry, Kim McCleary

MEETING AGENDA

11:00 – 11:05 am **Welcome Remarks**
Robert Rauner, *President, United Leukodystrophy Foundation*

11:05 – 11:15 am **About this Meeting: Review of Meeting Agenda and Desired Outcomes**
Kim McCleary, *Moderator* and Neel Odedara, *Co-Moderator*

11:15 – 11:30 am **Overview of the Diagnosis, Clinical Features, and Treatment of CTX**
P. Barton Duell, M.D., *Professor of Medicine, Oregon Health and Science University*

Session 1: Diagnostic Odyssey, Disease Symptoms, and Daily Impacts of CTX

11:30 – 11:55 am **Panelist Remarks: Living with CTX**
John Wolf, Sangna Odedara, Debra and Tom Johnson, and Sue Stewart

11:55 – 1:00 pm **Facilitated Discussion**
Each part of the discussion will start with a community perspective
Narinder Ghara, Catherine Zonsky, Shannon DeLaMar, Kay Fischer, and Austin Larson
Other community members are invited to call in live with comments: 1.703.844.3231

Key Questions:

- What were some of the challenges of getting appropriate attention in the search for a diagnosis?
- Of all the symptoms experienced, which 1 to 3 symptoms are the greatest burdens?
- What are the biggest concerns or worries related to CTX – both today and for the future?
- What are the greatest impacts on daily living for both the person with CTX and the family?

1:00 – 1:20 pm **Break**

Session 2: Current and Future Treatments for CTX

1:20 – 1:40 pm **Panelist Remarks: CTX Treatment Experiences**
Bobbi Blanchard, Robin Huard, and Shawn Laurie

1:40 – 2:35 pm **Facilitated Discussion**
Each part of the discussion will start with a community perspective
George Bryce, Avril Dimond, Holly Rosengrant, Estefania Amyerich, and Bob Steiner
Other community members are invited to call in live with comments: 1.703.844.3231

Key Questions:

- What therapies are being used to help treat CTX, relieve symptoms, or improve quality of life?
- Which 1-2 aspects of the condition are most important to relieve/control/reverse?
- What issues have affected access to therapy and what effects are seen when primary therapy with CDCA is interrupted?
- What has your experience been with regard to clinical trials or experimental therapies?
- What are the unmet treatment needs? What would you like to see in future treatments?

2:35 – 2:50 pm **Remarks from FDA: Value of PFDD in CTX and Themes Heard from the CTX Community**
Vijay Kumar, M.D., *Office of Tissues and Advanced Therapies, CBER, FDA*

2:50 – 3:00 pm **Final Closing Remarks**
Robert Rauner and Kim McCleary

The United Leukodystrophy Foundation

Leukodystrophies comprise a group of genetic nervous system disorders affecting the myelin sheath, which insulates the axon through which nerve impulses are conducted.

OUR MISSION is to provide support to the leukodystrophy community and enable platforms to accelerate improving patient quality of life and finding cures.

OUR VISION is to meet the needs of patients and families, whether newly diagnosed or living with a leukodystrophy. Through unified collaboration with advocacy groups, medical and research professionals, and pharma/biotech companies, we provide support, networking, and education to help navigate the journey of the disease.

About

Located in DeKalb, Illinois, the United Leukodystrophy Foundation (ULF), is a nonprofit, voluntary health organization dedicated to providing patients and their families with information about their disease and assistance in identifying sources of medical care, social services, and genetic counseling. The ULF works to establish a communication network among families; as well as increases public awareness and acts as an information source for health care providers by promoting and supporting research into causes, treatments, and prevention of the leukodystrophies. Incorporated in 1982, the United Leukodystrophy Foundation is solely supported and funded by donations.

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UNLOCK CTX

CEREBROTENDINOUS XANTHOMATOSIS

An initiative of the United Leukodystrophy Foundation