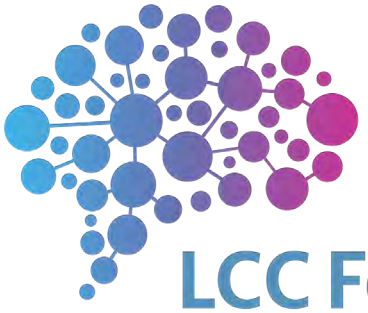

LCC Foundation

Leukoencephalopathy with Brain Calcifications & Cysts (LCC/Labrune Syndrome)

FDA Patient-Led Listening Session

Friday, July 11, 2025

10 am – 11:30 am ET

Session Summary

Summary of Topics Discussed

- Provide an overview of The LCC Foundation
- Provide a scientific overview of Leukoencephalopathy with Brain Calcifications & Cysts (LCC/Labrune Syndrome)
- Share the most common health concerns for LCC patients and their families
- Describe the most burdensome symptoms and impacts on quality of life for patients and their families
- Describe symptomatic treatments being used and the unmet medical needs

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Patients Represented

Two adult LCC patients spoke, as well as four parent/caregivers spoke, representing another 5 patients.

Medical Professional Speaker

Jamie L. Fraser, MD, PhD, Children's National Hospital, Washington, DC

FDA Divisions in Attendance

Office of the Commissioner (OC) – 2 offices

- OC/OEA/PES – Office of External Affairs/Public Engagement Staff (*organizer*)
- OC/OCMO/OPT – Office of the Chief Medical Officer/Office of Pediatric Therapeutics

Center for Biologics Evaluation and Research (CBER) – 3 offices

- CBER/OCD – Office of the Center Director
- CBER/OTP/OCE/DCEGM/GMB2 – Office of Therapeutic Products/Office of Clinical Evaluation/Division of Clinical Evaluation General Medicine/General Medicine Branch 2
- CBER/OTP/PSPS – Office of Therapeutic Products/Policy and Special Projects Staff

Center for Drug Evaluation and Research (CDER) – 8 offices

- CDER/OND/ODES/DCOA – Office of New Drugs/Office of Drug Evaluation Sciences/Division of Clinical Outcome Assessment
- CDER/OND/ON – Office of New Drugs/Office of Neuroscience

- CDER/OND/ON/DNI – Office of New Drugs/Office of Neuroscience/Division of Neuroscience I
- CDER/OND/ON/DNII – Office of New Drugs/Office of Neuroscience/Division of Neuroscience II
- CDER/OND/ORDPRUM/DRDMG – Office of New Drugs/Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine/Division of Rare Diseases and Medical Genetics
- CDER/OTS/OB/DBI – Office of Translational Science/Office of Biostatistics/Division of Biostatistics I
- CDER/OTS/OB/DBII – Office of Translational Sciences/Office of Biostatistics/Division of Biostatistics II
- CDER/OTS/OCP – Office of Translational Sciences/Office of Clinical Pharmacology

Center for Devices and Radiological Health (CDRH) – 6 offices

- CDRH/OPEQ/OHT1/DHT1C – Office of Product Evaluation and Quality/Office of Health Technology I/Division of Health Technology IC
- CDRH/OPEQ/OHT3 - Office of Product Evaluation and Quality/Office of Health Technology III
- CDRH/OPEQ/OHT3/DHT3B - Office of Product Evaluation and Quality/Office of Health Technology III/Division of Health Technology 3B
- CDRH/OPEQ/OHT3/DHT3C - Office of Product Evaluation and Quality/Office of Health Technology III/Division of Health Technology 3C
- CDRH/OPEQ/OHT3/DHT4C - Office of Product Evaluation and Quality/Office of Health Technology III/Division of Health Technology 4C
- CDRH/OSPTI/OEID/DCPD – Office of Strategic Partnerships and Technology Innovation/Office of Equity and Innovative Development/Division of Patient-Centered Development

Non-FDA Attendees

Reagan Udall Foundation

National Institutes of Health (NIH)

- NIH/NCATS – National Center for Advancing Translational Sciences

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Agenda

- Welcome & Introductions – FDA Patient Engagement Staff
- Motivations for this Session – The LCC Foundation
- The Overview of The LCC Foundation – The LCC Foundation
- What is LCC? – Dr. Jamie Fraser
- Patient/Caregiver Perspectives (6 speakers)
- Q & A – FDA
- Closing Remarks – FDA Patient Engagement Staff

Welcome by FDA Patient Engagement Staff

Brief welcome statement: We'll be hearing from patients, parents/caregivers, and advocates from the LCC community. There are three FDA Centers and the Office of the Commissioner in attendance. The financial disclosures were read aloud, to which there are none to report from The LCC Foundation and the LCC community speakers.

Motivations of This Session

We hope to provide the FDA with a deeper understanding of the critical challenges faced by the LCC/Labrune Syndrome community.

- The serious impacts of disease on LCC patients and their families.
- The effects on the patients' quality of life.

We hope to educate the FDA on the unmet medical needs of the LCC/Labrune Syndrome community.

- There are currently no FDA-approved treatments.
- We will discuss families' preferences for treatments and outcomes.

The LCC Foundation – Our Mission

The LCC Foundation is a US-based 501(c)(3) nonprofit organization, founded in April 2022. Our story began when families like mine faced the life-changing diagnosis of Leukoencephalopathy with Brain Calcifications and Cysts or LCC—a rare, progressive genetic disease. We realized very quickly that we needed more than just hope—we needed a community, resources and a path forward.

Our mission is clear: we proactively serve those affected by LCC through dedicated programs in Education, Research and Advocacy. These three pillars guide every decision we make. Through education, we help families understand this complex condition. We identify sources of medical care, social services, and genetic counseling, which are vital for families

navigating this rare disease. We also work to establish a communication forum where families can connect, share experiences and know they are not alone.

Raising awareness is another critical part of our work. We actively strive to increase public awareness so that LCC is recognized and diagnosed earlier—because early intervention and informed care can make a real difference.

We know that families and clinicians need reliable, up-to-date information. That's why we are creating information sources specifically for healthcare providers—so they can better understand, diagnose and manage LCC in their patients.

And finally, we are deeply committed to research. We partner with Dr. Jamie Fraser to promote research into the cause, treatment, and one day, the cure of LCC. We believe that research is the bridge that connects today's families to tomorrow's breakthroughs.

In just a short time, we have seen the power of community and collaboration. Families who once felt isolated now have a place to turn. Researchers who once knew little about this disease have new insights to build on. And the world is beginning to hear our voices.

The LCC Foundation exists because we believe every family deserves answers, support, and hope for the future. Together, we will keep working—until no family faces LCC alone.

Dr. Jamie Fraser – Scientific Landscape of LCC

Dr. Fraser is a biochemical geneticist and physician-scientist at Children's National Hospital in Washington, DC, where she serves as the lead principal investigator for research into LCC. With a strong focus on translational research in rare neurodegenerative diseases, Dr. Fraser brings both clinical expertise and scientific rigor to the study of LCC. Her leadership is instrumental in driving forward the understanding of disease mechanisms and exploring therapeutic pathways for this ultra-rare condition.

Dr. Fraser had no financial disclosures. She did state that when discussions of various clinical laboratory providers are named, it is for the purposes of demonstrating the scope of challenges in diagnosis.

Leukoencephalopathy with Calcifications and Cysts is clinically defined by white matter changes, brain calcifications and cysts. The signs and symptoms include Seizures, Movement Disorders and Loss of Functional Abilities. The location of the calcifications, cysts and white matter changes affect the presentation of the patient. Progression of the disorder may be due to abnormalities of the blood vessels, which is defined as microangiopathy.

From 1990's-Present: The observed changes in the brain morphology and histopathology suggest a neuroinflammatory contribution: white matter hyperintensity, calcifications, and cyst evolution and composition.

October 2016: LCC is linked to a gene. SNORD118 gene, which is part of the "U8 ribonucleoprotein complex."

The LCC Natural History Study began in 2018, as well as the first LCC Family & Research Conference. In 2019, the second LCC Family & Research Conference as held. In 2020, a Zebrafish Model System with mechanisms was started.

In 2021, LCC mice model was generated and the first Global LCC Family Conference was held via Zoom. In April of 2022, The LCC Foundation incorporated as a 501(c)(3) nonprofit organization.

In 2024, Integrated Stress Response (ISR) was described as a potential mechanism of the disorder.

LCC Research was first presented to the Global Leukodystrophy Initiative-Clinical Trials Network in 2025, as well as the Children's National Hospital Natural History Study of LCC Manuscript drafted in the summer of 2025.

Genetics & Prevalence: LCC is autosomal recessive, biallelic pathogenic variants in the SNORD118 gene. It is an ultra-rare neurological disorder, affecting less than 100 published patients worldwide. There are compound heterozygous, bi-allelic variants and these variants are observed in critical regions of the snoRNA structure.

Mechanism: SNORD118 gene is part of the "U8 ribonucleoprotein complex." It is considered a ribosomopathy, which is a disorder of the ribosome. There is insufficient protein production. It affects "translationopathy," oligodendrocytes and other non-neuronal central nervous system cells. Other similar conditions include Vanishing White Matter, PolR3, tRNA Synthetase Disorders (DARS1, RARS1, EPRS1), Interferon activation and other inflammatory processes.

Why the Brain? Only the Brain?

The brain is a high energy system that is specialized protein machinery. Our bodies have the Blood-Brain-Barrier, which has special endothelial cells and other cell types in the central nervous system with extra protein machinery. The mechanism isn't well understood for LCC. There is p53 activation, integrated stress response, microangiopathy and inflammation.

Diagnosis:

SNORD118 is not routinely identified on Whole Exome Sequence/Panels. Whole exome sequencing technologies and request of information is highly variable. I must specifically request this testing for GeneDx. The Ambry lab does not detect/report. Invitae lab varies based on genotype. Their panel will miss significant variants. Whole genome sequencing will detect SNORD118. It helps to request this testing: SNORD118/TMEM107.

Natural History Study: Clinical Cohort

We have enrolled 33 patients from 26 families. We conducted detailed phenotyping on 29 patients between the ages of 2-45 years. We have 31 patients that are currently alive. We have a natural history study. We are conducting an MRI review. We have neurological and functional assessments. We have specimen biobanking.

Disease-Onset & Symptoms

LCC presents first with white matter changes, brain calcifications and cysts show up later in the course of the disease.

Epilepsy Management

According to the natural history study on LCC/Labrune Syndrome, 3 out of 21 patients reported no seizures. 5 out of 21 patients reported that their seizures had resolved and were

currently not on any anti-seizure medication. 4 out of 21 patients reported taking 1 anti-seizure medication. 7 out of 21 patients reported taking 2 or more anti-seizure medications. And 2 out of 21 patients reported taking anti-seizure medication and non-prescription therapy was being used.

Natural History Summary

Prematurity or Fetal Growth Restriction and epilepsy before their first birthday are the earliest hallmarks of disease. Cerebral Palsy symptoms and developmental delay are seen. MRI can be normal early in life, but then white matter changes and calcifications are seen, and then later stage disease, the cysts are seen. Seizures are typically focal, and the treatment may be complex. Patients experience growth and fatigue. Patients also experience mental health symptoms such as: ADHD, executive dysfunction, anxiety, depression and hallucinations. Movement disorders are common and may be concurrent. They are a significant source of morbidity. The medical management for movement disorder is chemical denervation and sometimes deep brain stimulation utility. Cyst intervention (when feasible) temporizes functional impairment and alleviates symptoms.

Management

For epilepsy management: multiple drugs may be needed. Seizures may worsen over time due to new calcifications, cyst development or enlargement. If there is worsening or new semiology, I recommend a repeat MRI. Movement disorders are common and involve movement disorders specialist to optimize regimen. Use caution when considering deep brain stimulation. Cyst intervention should be considered with acute worsening of symptoms or increased intracranial pressure. For acute interventions, it is recommended to do direct drainage, external drain. Omaya reservoir versus tappable cystoperitoneal (CP) shunt for recurrent or life-threatening cysts. Ventriculoperitoneal (VP) shunt is recommended for secondary hydrocephalus. It is recommended that MRI imaging is done in regular intervals after diagnosis. If there is no cyst seen on imaging, I recommend imaging every 12 months. If there is a cyst present, I recommend repeat imaging every 6 months. Recommend including contrast when feasible to visualize acute inflammation. Images with acute clinical change that includes cyst enlargement or new cyst development may require urgent intervention. If

there is acute disease progression, it recommended to prescribe corticosteroids. Chronic treatment includes Bevacizumab (Avastin), which there is highly variable evidence for short or long-term effect. Intra-cystic hemorrhage is a risk and is microangiopathy a late finding? Other immunomodulators: off-label use in steroid-responsive disease. Long-term use (greater than a year) efficacy not established. Drug repurposing clinical trial in development to establish efficacy for LCC. Other management should follow clinical guidelines for care of patients with leukodystrophies. Bonkowsky, J. (2017) "Leukodystrophies in Children: Diagnosis, Care and Treatment." Journal of Molecular Genetics and Metabolism 122 (2017) 18-22. https://www.sciencedirect.com/science/article/abs/pii/S1096719217303724#preview-section-abstract.

Critical Unmet Needs

We need increased awareness. Earlier identification for adults and children. Improved clinical testing access—exome and panel options not all reliable. Variant of Uncertain Significance in SNORD118 and disease association and missing second variant issues. We need increased understanding of mechanisms, pathways, and modifiers of disease. We need funding for generic drug repurposing clinical trials. We need safe and effective treatments and/or a cure. Our pathway going forward is to arrest progression that gets our patients to a gene/RNA therapy.

Myelin Disorders Clinical Research Program Team includes:

Laura Tochen, MD; Jullie Rhee, CPNP-AC; Miriam Bloom, MD; Mi Ran Shin, MD; Jason Schroeder, MD; and Nimisha Bajaj, MD, PhD.

Patient & Family Perspectives

Two patients presented their journeys, as well as 4 parents/caregivers, representing 5 patients, presented their families' journeys.

Adult LCC Patient 1, Speaker 1

Thank you for taking the time to hear my story and understand what a therapy could mean—not just for me, but for others like me.

I've lived my entire life with a rare condition called leukoencephalopathy with calcifications and cysts. It's a long name, but what it means is that my brain has areas that have hardened—calcified—and there are cysts, or fluid-filled sacs, that can affect how my brain functions. It's not something you hear about often. In fact, when I was first diagnosed, no one really knew what it was or what to expect.

My journey started when I was just a baby—3 months old—when I had my first seizure. That moment changed everything. I was put on strong anti-seizure medications as an infant. Thankfully, the seizures stopped after a year, and for a little while, everything seemed okay. My parents thought they had made it through the worst, and so did I. But around the age of four, I began to struggle again—this time, not with seizures, but with overwhelming anxiety, especially when it came to going to school. I just couldn't handle it. The emotions, the fear—it was something I didn't understand, and neither did the people around me.

During therapy, my doctor recommended a brain MRI—not because they suspected anything specific, but just to get a baseline. They wanted to be safe, especially since anxiety medications can sometimes affect the brain at that age. That scan changed everything. It showed calcifications and cysts in my brain. No one knew what to make of it. The doctors were puzzled, and we were scared.

From that moment forward, my family and I were thrown into years of testing, referrals, second opinions, and more questions than answers. We traveled up and down the East Coast, seeing specialists, getting poked and scanned and studied. And through all of it, we still don't know what we were facing. Along the way, my youngest sister started having trouble at school, too. Because of my diagnosis, her doctor ordered an MRI just to rule things out—and that's when we found out she had the same cysts and calcifications.

That discovery shifted everything for us. It wasn't just about me anymore. We knew we were dealing with something genetic, something shared, something much bigger. Eventually, we

became part of a clinical trial at Johns Hopkins, working with Dr. Crow, a researcher based in the UK. It was in that study that they finally discovered the DNA sequence causing our condition. That moment gave us something we hadn't had before—clarity. A name for what we were fighting. A starting point for real answers. Since then, we've been working closely with Dr. Fraser and her team at Children's National, who've continued to support us and help us manage our care.

Living with this condition has affected nearly every part of my life—my health, my education, and even decisions about my future. One of the hardest decisions I've made was to have my tubes tied. It wasn't something I took lightly, but I had to be realistic. I knew that with the unpredictability of my disease, the risk of pregnancy, and the long-term demands of caring for a child. I might not be able to give a child the life they deserve—or protect my own health in the process. That was a decision I made out of love and responsibility, not regret. But it was one of the many ways this disease has shaped my life.

So, when I hear about gene therapy—about the possibility that this disease might be slowed, stopped, or even reversed—I don't just hear medical terms. I hear hope. I hear the chance to live a life with fewer interruptions, fewer hospital visits, fewer missed opportunities. I hear the chance to feel like everyone else, even just a little bit.

I approach therapy with an open mind and a deep desire to learn everything I can. I want to know the risks. I want to understand the benefits. I'm not naïve—I know nothing in medicine comes with guarantees. But I also know what I've lived through. I know what it feels like to have a disease that no one fully understands. I've had to come to terms with my diagnosis. There are days where I forget—where I live life and feel almost normal. And then there are days where I'm reminded, in the hardest ways, of what I'm up against. Despite that, I've made peace with this condition. But just because I've accepted it doesn't mean I'm giving up. I welcome every opportunity for progress, every chance to improve my life—and maybe even help others along the way.

If a clinical trial could offer even a small improvement—just a few more good days, fewer symptoms, or a little more independence—that would mean everything to me. I believe in starting with lower doses to reduce the risk of side effects, and I want to understand how any

early-stage treatment might impact what's possible in the future. I want to make smart, informed choices about my care. But I also don't want to miss a window of opportunity. Right now, my symptoms are noticeable but manageable. I believe I could be a strong candidate to help test how early treatment might work—and what it might make possible.

This disease has been hard on my family. When my sister and I were diagnosed, we were told it was terminal. Those are words that change a family. But being part of a trial would bring something back that we lost for a long time—hope. Not just for survival, but for living. For quality of life. For better days ahead.

We are open to continuing to work with researchers after the trial. We want to help, not just for us, but for everyone else who might get this diagnosis tomorrow or next year or five years from now. We believe in moving things forward.

What I want most is a chance at normalcy. I don't expect a miracle. But I want fewer days of fear, fewer missed milestones, fewer moments lost to seizures or symptoms. I want to be able to live a full life—with stability, independence, and dignity. If this therapy can help me get there, even a little, then I want to be a part of it.

Thank you for listening to my story. Thank you for considering what a therapy means to people like me. Your work gives families like mine a reason to believe in something better.

Main Symptoms

- Seizures
- Mood Disorder
- Tremors
- Dystonia

Parent/Caregiver to two LCC patients, Speaker 2

We are a family of six with four sons — two of whom have been diagnosed with LCC (Leukoencephalopathy with Brain Calcifications and Cysts). Our story centers around our third-born son, who began his medical journey at just 6 months old after experiencing a series of seizures. That began years of testing and supportive therapies before we finally received a

diagnosis of LCC when he was 8 years old — a path all too familiar to families affected by ultra-rare diseases.

Our third-born is a complex patient with high medical needs. Much of what we share about life with LCC is centered around him. In the early years, he continued to hit developmental milestones, but they were delayed. Over time, we've watched with heartbreak as abilities he once had — walking, running, playing with his brothers, even talking — have slowly been taken away. He progressed from walking with orthotics to using a walker and is now completely wheelchair dependent. Adapting to his ever-changing needs has been one of our greatest challenges — technology and equipment evolve, but so do his needs, which means constant adjustments, additions, and modifications.

Many LCC concerns are movement related. For our son, this includes spasticity and dystonia. Every day we work to address issues like posture, head control, and safe positioning — in his chair, at meals, during transfers, and in bed. He has used walkers, standers, communication devices, and multiple wheelchairs. But no equipment or plan is ever final — his body's changes demand constant problem solving.

Creating normalcy for the whole family is a constant effort. We still make sure our teenager gets to the mall or the gym, and our club soccer player to practices and games. We carry our son into the stands to watch his older brother play in the marching band. We support him in the pool, making sure he can take part in family fun.

Daily life involves countless tasks that cannot be skipped:

- He takes multiple medications three times daily, which involves dissolving pills and administering them through a g-tube.
- He enjoys meals with the family, but because he can't consume enough orally, he receives nutritional supplements through his g-tube three times a day.

- He needs help with toileting, showering, changing clothes (three to four times a day), oral hygiene, and a bedtime routine that includes managing dystonic spasms that interrupt sleep.

The demands of LCC leave little room for caregivers to care for themselves. It's easy to neglect exercise, eat poorly, and have little time to nurture relationships. This can strain marriages, limit time with extended family, and isolate friendships.

Last summer, we learned through genetic testing that our oldest son also has LCC. He is 16 — driving, working, starting his junior year of high school, playing in the band, and has a girlfriend. He is asymptomatic, with only minor brain calcifications stable on MRI. We strive to protect his sense of normal and balance our worries about what the future may bring.

Our second-born and youngest sons are carriers. We work hard to ensure their childhood is not overshadowed by LCC or caregiving demands.

In summary, we hold hope for the future. We ask FDA and stakeholders to help move this hope forward by:

- Supporting clear pathways for LCC research and drug development. The loss of the PRV (Priority Review Voucher) program was a setback for rare diseases; a version of it under Makary offers new hope.
- Incentivizing development for unmet needs and repurposing existing molecules.
- Encouraging innovation such as AI to help identify new treatment options.
- Prioritizing new therapies that manage symptoms or slow/halt progression.
- Carefully weighing risk versus benefit for new therapies — and possible future gene therapy — on a patient-by-patient basis.

Our family's journey with LCC is one of relentless challenges and unwavering love. We ask for your continued commitment so that one day, families like ours have more answers, more support, and more hope for the future.

Parent/Caregiver to 17-year-old LCC Patient, Speaker 3

I'm here to speak on behalf of our 17-year-old son, who has Labrune Syndrome.

He was born prematurely at 32 ½ weeks and spent 3 weeks in the NICU due to feeding difficulties. When we brought him home, we thought the worst was behind us. But at 4 months old, he began having seizures—brief, frequent twitching in his face or hand, up to 30 times a day. We were told this could by typical for preemies and that he might grow out of it. He was put on phenobarbital, which stopped the seizures, but the side effects were devastating. He didn't crawl, babble, or reach typical milestones during the nine months he was on the medication. Once we took him off it, he began to catch up—slowly. Again, we allowed ourselves to believe that everything would be okay.

In early childhood, he began to struggle in school. He qualified for special needs preschool due to speech delays and developmental differences. By second grade, his teachers suggested he might have ADHD—he had difficulty focusing and controlling impulsive behavior. He was evaluated and diagnosed, and we started him on Focalin. It helped somewhat, and again, we believed these were manageable challenges.

But everything changed in May 2017. Just before the end of third grade, he had a grand mal seizure. A precautionary CT scan revealed bleeding, calcification, and a cyst in his brain. We were referred to Children's National Hospital in Washington, DC., where we received the diagnosis: Labrune Syndrome. Genetic testing confirmed it—he had the condition; the rest of our family did not.

We soon learned that the largest cyst was in the front left part of his brain—an area responsible for impulse control. That's when we understood he never had ADHD. What we thought was a behavioral condition was actually a symptom of structural damage in his brain. We stopped the medication, but the reality had shifted. We were no longer managing developmental delays—we were confronting a degenerative brain disorder.

Even after the diagnosis, we clung to hope. Our son stayed in mainstream classes through fifth grade with the support of an Individualized Education Program (IEP). But that year marked a turning point. He began falling behind—academically, socially, emotionally. In middle school, he moved to a special education classroom with a slower pace. By seventh grade, even that wasn't enough. He eventually transitioned into a life skills classroom for students with more significant needs.

He became what one educator called an "in-betweener"—too disabled for traditional classes, but too high-functioning to fully connect with peers in life skills. His speech deteriorated. His motor skills declined. He withdrew socially. We started to realize he might never graduate high school, never live independently, never follow the path we imagined for him.

And the disease hasn't stopped. What started as one large cyst has now become about 20 cysts—6 of them large. The calcification in his brain has also increased. It is relentless, and we can see it taking more of him every year.

Then came the pandemic. During eighth grade, remote learning brought a surprising relief—he was happier at home. But when in-person learning resumed in ninth grade, he refused to go back. School had become too overwhelming, too isolating. His speech was nearly unintelligible. His motor skills were slipping. He no longer fit in anywhere—too impaired for one setting, but too aware for another. For the first time, we fully accepted that he would never have a "normal" life.

He should be preparing for his senior year right now. Instead, he stays home where he feels safe. His one remaining joy is video games—but even that is becoming difficult as his hands weaken.

He once had friends. He played football. Rode his bike. Went on family outings. Now he has no friends, and his only interest—gaming—is slipping away. His body is failing him. His speech, one 90% intelligible, is now closer to 10%. He's lost use of his dominant left hand. His left ankle is turning under and will soon no longer support him. He uses a wheelchair for distances longer than 100 yards.

He cannot be left alone. He needs help with nearly everything—bathing, dressing, preparing meals. He can eat independently only if food is soft or cut small, and someone must watch him in case he chokes. He only drinks in front of the kitchen sink because liquids often come out of his mouth and nose. He can no longer use a straw due to muscle loss in his mouth. He takes three anti-seizure medications, twice a day. His seizures are unpredictable. He tires easily, gets headaches and sometimes collapses unexpectedly.

And yet, perhaps the hardest part is that he knows. He knows he's different. Every Christmas, he asks Santa for a new brain. He understands he has Labrune Syndrome, but he doesn't know how it ends. That, in some way, is a blessing. Because watching your child trapped in this "in-between" space is one of the hardest things a parent can endure. He's aware enough to want a normal life. He wants friends. He wants freedom from medication. And there is nothing we can do to give him that.

What we ask of the FDA is a chance. The opportunity to participate in a trial. Even the hope of small improvement is enough. We know there may not be a cure—but we hold on to any thread of possibility that could slow this disease, that could preserve some part of our son's joy, his voice, his movement.

Thank you for listening to our story.

Adult LCC Patient 2, Speaker 4

Thank you for taking the time to hear about LCC and how it affects patients like me.

I was diagnosed with LCC at age 11, after many visits with doctors and specialists who were trying to understand why I had started having seizures. In addition to seizures, my parents and teachers were trying to figure out why I struggled with certain subjects in school. We didn't know then how these things were connected.

My journey with LCC began in Central California. I was born in Santa Cruz, California and lived there until I was 10 years old. Like my older brother, I had seizures when I was a very young baby, but after a few months I outgrew them and was eventually taken off medication. I also had some challenges in elementary school, mostly related to visual learning, such as mixing up the order of letters in a word, or certain types of math problems. I needed extra help and

resources to keep up with the curriculum. But despite those challenges, I was a happy and active kid who had a lot of fun and was involved in lots of interesting hobbies like soccer, bike riding, playing tennis, going to the beach, Girl Scouts, Japanese Drumming, and taking care of my guinea pigs, chickens, dog and cat. Life was pretty good.

Then, at age 10, I began to have seizures again. Doctors in California did tests but were unable to find a specific cause, probably because this was in 2016 before the cause of LCC had been discovered and published. I was put on medication to try and control the seizures. Then we moved back to Nova Scotia, Canada, in 2017. Soon after we moved, an MRI image showed that the white matter in my brain looked very strange. My neurologist communicated with colleagues to see if any of them knew what kind of white matter disease this could be. At the same time, I was having genetic tests done. And then, after the 3rd set of tests, they found that I had a mutation of the SNORD118 gene. Doctors told me and my family that I had a rare, recently discovered disease called Labrune Syndrome, now called Leukoencephalopathy with Calcifications and Cysts (I have trouble saying those words, so I usually just say LCC). From that moment on, we have been trying to learn more about this disease and its symptoms, and whether there could one day be a cure. We found that there was very little information available. We met some other families of kids with LCC through social media groups, where we were able to get a bit more information. By talking with other families and their doctors we found that there were many patterns that were similar between us. No two of us have identical situations, but we have things in common such as how the disease progressed, and how it affected things like our learning or speech or balance. We were told by neurologists that our symptoms depended on where exactly the cysts formed, and how fast they grew, and what other parts of the brain they were putting pressure on. In my particular case, as well as causing seizures, LCC affects my vision and cognition, especially things like visual-spatial processing and the ability to retain things that I have read.

I am now 19 and just completed high school. I have been taking a variety of anti-seizure medications for about 8 years now, with varying levels of success. Sometimes I can go many months without a seizure, but other times there can be a bunch over a few weeks. Some seizures are small and localized, but others can be large tonic-clonic seizures that involve

ambulances being called. This has been pretty hard to handle as a high school student, although I am lucky to have some amazing friends who always support me through everything. I work really hard academically to overcome learning challenges of LCC. Focusing while at school is literally exhausting, and I am told by my neurologist that this is expected because calcification and cysts in my white matter cause signal transmissions in my brain to be lost, so my brain is working many times harder than normal to compensate. So, when I get home from school, I am usually exhausted and often need a nap before starting on homework. With hard work and support systems and some amazing teachers who were able to figure out my specific ways of learning, I was still able to attend regular classes and achieve decent grades. I think this is partly because I just really love learning. I am proud to be graduating, although I am sad that my school years are finishing.

Despite these successes, there have also been major hurdles, and I feel like they are increasing over time. I often feel quite alone with the condition, which is impossible to explain to my friends, family, teachers, and even many of the doctors who I go to see. I have much less independence than most kids my age: my seizures mean I can never drive, or do many activities, and I can't really be alone without somebody nearby. It is scary for me that there is no real treatment available, no cure to shrink or get rid of the calcifications and cysts in my brain, and it is slowly getting harder to do some of the things I was doing 5 or 10 years ago.

My mental health has definitely been impacted over the past few years. I suffer from a lot of anxiety. I know that many high school students suffer from anxiety, but for me the usual social anxieties are on top of anxieties about seizures and uncertainty about my health and future. Over the last two years I have been diagnosed with and treated for, both OCD and Anorexia, and I know both of these disorders were related to my LCC. Having a disease that you have no control over is very hard, and impacts not just me, but my whole family.

We are still figuring out a path for my future, which we try to be optimistic about, but sometimes that is hard too. Knowing that there is work being done that will eventually lead to an effective treatment is really important to me. The things I want most from a treatment are relief from the symptoms that impact me most: I would love not to have seizures. I would

love not to be so exhausted all the time. I would love to be able to be physically active, and to participate in more activities. Most importantly, I want to have more independence, and to look forward to a full and productive life with family and friends.

I want to do everything I can to help with getting to such a treatment, both for myself and for all the other kids that also have this rare condition.

Parent/Caregiver to 5-year-old LCC Patient, Speaker 5

Good morning and thank you for the opportunity to speak with you today.

I'm here as a mother of a strong, and deeply loved little boy, who lives every day with a condition known as LCC. For those of you who may not be familiar, LCC is an extremely rare genetic neurodegenerative disease characterized by brain calcifications and cysts. Our son has calcifications, but as of today, no cysts—something we're grateful for, while remaining cautiously aware of the progressive nature of this condition.

I want to take this time to walk you through what our day-to-day life looks like, not just as a list of symptoms and appointments, but as a family navigating the full emotional and physical reality of caring for a child with LCC. Because behind every rare diagnosis is a family trying to hold everything together.

Our son's symptoms affect nearly every aspect of his life. He has left-sided hemiplegia and spasticity, which means his muscle control and movement on that side are limited and often painful. He wears an AFO—an ankle-foot orthosis—and uses a wheelchair when needed. He takes Baclofen to help with the muscle stiffness, but the effects are modest and temporary.

He has developmental delays, wears glasses, and also an eye patch for his wandering left eye. Like many children with complex conditions, he also has scoliosis, which adds to his physical challenges.

Three days a week, we're in therapy. Physical, occupational and speech—each session is a step forward, but also a drain on time, energy, and sometimes hope. The other two days?

Usually reserved for specialist appointments. Neurologists, orthopedists, Botox, yearly MRIs, and ophthalmologists—you name it. There is no such thing as a free day in our week.

My husband is active-duty military and if you're familiar with military culture, you'll recognize the phrase: "Mission First." He shows up for our family every chance he gets, but the reality is that I shoulder most of the responsibilities related to our son's condition.

As a stay-at-home mom of two children—soon to be three—that means managing every appointment, every form, every conversation with insurance or specialists. And more than anything, the guilt that comes with not being able to split your time and energy evenly among all your children.

One of the hardest parts of this journey isn't just our son's condition—it's how little time and energy we have left over for our other kids/life activities. When your life revolves around getting one child the care they need just to function, it can feel like you're always falling short somewhere else.

People often ask me, "How do you do it?" and the truth is – I don't always know. There are good and bad days. Our son has a sense of humor that lights up the room. His resilience is contagious. But there are also days filled with uncertainty, grief and the quiet mourning of the life we imagined for our son before we ever heard the words "Labrune Syndrome, also known as LCC."

When people ask about a cure or treatment, my answer is simple. I would love one. A treatment or cure would offer hope for a more normal life for our son and the whole family. It would give him the chance to experience childhood like his peers, free from limitations and the feeling of being different especially at such a young age. More importantly, as a parent I want to prioritize his safety when it comes to a cure/treatment, starting cautiously with small doses and frequent monitoring. Right now, our son is doing relatively well. But LCC is progressive. We know that harder days may lie ahead. And like any parent, I want the option of hope—not just emotionally, but medically.

A cure might not come tomorrow or even in our son's lifetime, but continued research, awareness and support from the medical and scientific communities' matter. Because every

step toward understanding LCC is a step toward giving children/people like our son a better chance.

If there's one thing I hope you take away from our story, it's this: behind every chart, every diagnosis, every scan, is a family working tirelessly to keep going. We aren't just managing a disease, we're living a life – one filled with love, exhaustion, joy, grief, and constant adaptation.

And if I could just leave you with one thing, it would be to never underestimate the impact you have, not just on patients, but on the entire system of people who love and. Care for them. You are a critical part of our journey—and our hope.

Thank you so much for listening to our story. It's not an easy road, but it's ours—and we walk it with as much strength and hope as we can.

Parent/Caregiver to 11-year-old LCC Patient, Living in Mexico, Speaker 6

Our daughter is 11 years old. Her daily life is filled with music, dance and singing—each moment a celebration of movement and the joy she finds in expressing herself. Behind her radiant smile, however, is a story of resilience in the face of a rare and complex neurological disorder that began impacting her life at the age of three.

At that time, she began experiencing seizures. What followed was a long and uncertain diagnostic journey marked by uncontrolled epilepsy, motor skill difficulties, and years of inconclusive evaluations. After more than five years of misdiagnoses and unanswered questions, whole-exome sequencing finally provided clarity: she was diagnosed with Leukoencephalopathy with Calcifications and Cysts (LCC), a rare, progressive, and poorly understood neurological disorder.

Despite multiple therapeutic interventions, her epilepsy remains drug-resistant. At age 7, additional complications arose: chronic constipation, dermatological issues, persistent fatigue, and signs of precocious puberty. She was subsequently diagnosed with central

hypothyroidism and precocious puberty and later confirmed to have an intellectual disability. These findings necessitate personalized educational support and tailored learning strategies.

Her current treatment is symptomatic and palliative. Her daily regimen includes medications for epilepsy, hypothyroidism, constipation, and hormonal regulation. In addition, she participates in multiple supportive therapies: fine motor skill development through art, physical therapy for strength and coordination, academic support through Kumon, and neuropsychological therapy to foster cognitive and emotional development.

All these efforts are driven by a single objective: to ensure the highest possible quality of life and to slow the progressive neurodegeneration that threatens her independence and vital functions.

We are fortunate to count on the support of The LCC Foundation, Dr. Jamie Fraser, Dr. Andrea Quiroz and a committed team of therapists. However, significant unmet needs remain. There are currently no disease-modifying therapies for LCC, and research into its underlying mechanisms and potential treatments is critically limited.

We urgently need to:

- Advance scientific understanding of LCC and similar leukodystrophies.
- Accelerate the development of targeted therapies.
- Improve diagnostic pathways to prevent years of uncertainty for other families.
- Recognize the burden of rare pediatric neurological disorders and include them in broader research and regulatory frameworks.

Our daughter is not giving up. She continues to dance, sing, and embrace life with courage and joy. But she—and others like her—need the support of the broader medical and scientific community.

Supporting research and regulatory attention is giving our daughter a chance to live with freedom, health and hope.

Closing Remarks from The LCC Foundation

In preparation for this session, the LCC community who were unable to attend, were asked to share their voices. Their messages were represented on a slide. Words such as uncertainty, frustration, isolation, fatigue, and hope were listed. The specific quote at the bottom of the slide was referenced: "My children are square pegs which the healthcare system insists on trying to fit into round holes." We need your partnership to reimagine a system where our square pegs aren't forced to change shape—but where regulatory pathways bend to meet the urgent, unique needs of rare disease families, like ours.

FDA Question & Answer

Due to time constraints, the question-and-answer session with the FDA was not held as planned. The Public Engagement staff requested that any questions from the FDA for our community be submitted to them directly, and they will ensure they are forwarded to us for response. ForPatients@FDA.HHS.gov

FDA Staff: "Thank you for sharing your perspectives!"

"Thank you for sharing your experiences."

"Thank you to the patients and parents and Dr. Fraser."

Closing Remarks from the FDA

Thank you for bringing the voice of the LCC/Labrune Syndrome patient community to FDA this morning! We truly appreciate that you were so willing to take time out of your day to share your experiences, perspectives, and concerns around LCC/Labrune Syndrome with the FDA. We recognize how difficult it is to share personal experiences, and all of us on the call are incredibly grateful for everyone's willingness to share with us so openly. Hearing your perspective is critical to ensuring that the FDA can better understand LCC/Labrune Syndrome.

Disclaimer

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