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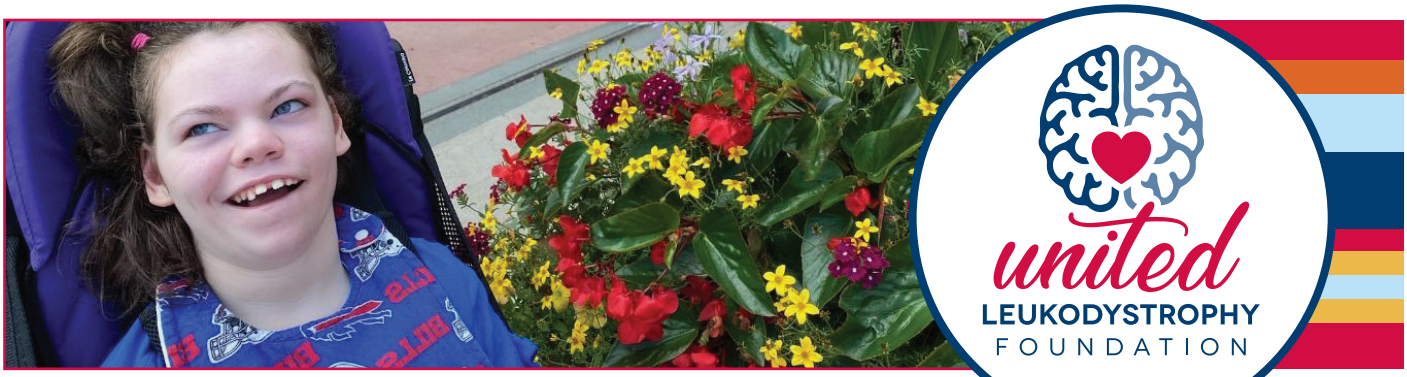
NEWSLETTER



12 NUMBERS TO CHANGE LIVES

On October 1, twelve new ICD-10 code numbers went into effect for the medical community.

What does this mean for the leukodystrophy community?

What does this mean for insurance companies?

What does this mean for researchers?

The ULF is proud to host a live webinar on **Wednesday, November 8th**, where Dr. Josh Bonkowsky and Monika Baker of University of Utah Health will detail their journey on securing these twelve numbers to provide a brighter future for leukodystrophy patients around the world. They will also answer your questions about what these codes could mean specifically for your family, and give suggestions on how to use these codes to advocate for better care options.

NEW ICD-10 CODES WEBINAR ON ZOOM

REGISTER: ULF.ORG/NEWS

This session will be recorded and posted to the ULF Office YouTube channel on Thursday, November 9.

Wednesday • November 8, 2023 • 1 PM E / 12 PM C / 11 AM M / 10 AM P

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A LETTER FROM THE PRESIDENT OF THE BOARD

I trust this message finds you well and filled with the same sense of hope and purpose that we with the ULF have. As we navigate the changing seasons, I am delighted to share some exciting updates and initiatives with you in this quarterly newsletter.

Left to right: Ron Chapleau (ULF), Marla Chapleau (ULF), Melody Kisor (Cure LBSL), Erica Barnes (Chloe's Fight Rare Disease Foundation), Marilyn Schmiedel (ULF), and Bob Rauner (ULF)

First and foremost, it is my pleasure to announce the arrival of our new Executive Director, Diane Fennimore. Diane joined our team in early September, and I am thrilled to report that she has exceeded all our expectations as a leader. Her dedication, expertise, and passion for our cause has already left an indelible mark. Diane comes to us after succeeding in a broad range of leadership roles over more than twenty years with such prestigious organizations as the American Cancer Society, Community Health Charities of New York and Women Corporate Directors Foundation among others. With Diane at the helm, we are confident in the bright future that lies ahead for the United Leukodystrophy Foundation.

There are also exciting developments when it comes to enhancing the lives and research efforts of all of us in the leukodystrophy community. Dr. Josh Bonkowsky, a member of our Medical and Science Advisory Board, and his team at the University of Utah have managed to gain approval for 12 new ICD-10 codes for individual leukodystrophies from the World Health Organization. Being granted this many codes at one time is almost unprecedented. These codes are invaluable in a multitude of ways. First, by having your various health service providers attach them to your charts, it greatly enhances the chances that insurance companies will pay for the services rendered to you. As many of us know, challenges with insurance companies can cause financial hardships and be just one more obstacle in a busy life that is already too full from the burdens these diseases impose upon us. As well, the ICD-10 codes are utilized by physicians and researchers from all over the world to track diseases, severity of progression, treatment outcomes, and more. Ultimately having these twelve new codes will result in faster diagnoses, more thorough treatment plans, and overall improved quality of life. We were thrilled to be asked by GLIA-CTN to help spread the word about this important breakthrough.

Lastly, I was thrilled to attend the National Organization for Rare Diseases (NORD) Summit in October with my wife, Marla, and many other leukodystrophy advocates. The ULF purchased a booth and invited all of our partner leukodystrophy organizations to join us there; spreading awareness about the disease and our organizations, and distributing the universal leukodystrophy brochure we designed that was written by neurologists for neurologists. Together, we are focusing our energies on an initiative aimed at educating the men and women that diagnose our loved ones. Our shared goal is to decrease the number of misdiagnoses and shorten the often brutal timelines before a proper diagnosis is achieved. This collaboration underscores the power of unity within the rare disease community and our shared commitment to improving the diagnostic journey for individuals facing leukodystrophies.

As we celebrate these milestones, it's crucial to acknowledge the invaluable support and dedication of our community members. Your commitment, resilience and passion continue to drive our mission forward and I am excited about the journey that lies ahead. Together, we are making a difference in the lives of those affected by leukodystrophies.

Best wishes to all,

RON CHAPLEAU

ULF Board President

THE UNITED LEUKODYSTROPHY FOUNDATION WELCOMES NEW EXECUTIVE DIRECTOR

The United Leukodystrophy Foundation is pleased to announce the appointment of Diane Fennimore as its new Executive Director.

Fennimore is a seasoned business development executive with more than twenty years of leadership experience in mission-driven organizations. She has a deep understanding of the strategies and partnerships that are critical to the success of advocacy initiatives, education, program development, research, and patient and family services. In September 2023, Fennimore will take the helm to support the ULF's work toward providing support to the leukodystrophy community, improving patient quality of life, and finding cures.

"I am honored to join the United Leukodystrophy Foundation as the new Executive Director," shared Fennimore. "I am excited to collaborate with our Board and staff to drive positive change and make a difference in the lives of patients and their families. I am looking forward to partnering with other leukodystrophy Patient Advocacy Groups, advancing relationships within the medical and research community, and contributing to the continued success and growth of the ULF."

Fennimore has demonstrated her passion for supporting women and children, and for elevating underrepresented and underserved people through developing creative collaborations with organizations that have similar priorities. Fennimore began her nonprofit career as the Senior Director of Corporate Development for the American Cancer Society. She set the strategic direction and led the execution of the Corporate Development program throughout New Jersey and recruited New Jersey's leading CEOs into a unique, multi-year partnership program.

Fennimore then served as President and CEO of Community Health Charities of New York (CHC-NY) where she reported to the Board of Directors and managed the operations, administration, and fundraising of CHC-NY, a membership organization of 165 health non-profits that delivered patient and family services throughout the state. In her role as the Vice President of Development at the Alliance for a Healthier Generation, Fennimore led the national diversified fundraising strategy that enabled the organization to deliver education and resources to schools and families nationwide to promote health, well-being, and academic success.

In her most recent role as the Development Executive at Women Corporate Directors Foundation, Fennimore promoted the advancement of gender diversity and women of color on Boards through creating collaborations with corporations.

Fennimore is a graduate of Fairleigh Dickinson University with an MBA in Marketing and holds a BS in Business Administration from Caldwell University, both located in New Jersey.

Ron Chapleau, President of the ULF Board of Directors, shared his enthusiasm for the new addition to the team: "I am delighted on behalf of our Board and the entire United Leukodystrophy Foundation family to welcome Diane Fennimore to our community as our new Executive Director. It was immediately apparent that Diane possesses a rare combination of drive, intellect, and business acumen; coupled with a generous helping of empathy and compassion that are essential to running a rare disease charity. Diane's long and successful history of leading other organizations assures a bright future for the ULF and the community we serve."

The ULF eagerly anticipates the unfolding of this new era of working together for positive outcomes in the leukodystrophy community.

FOR IMMEDIATE RELEASE September 29, 2023

Twelve New ICD-10 Codes For Leukodystrophies

Today marks a huge leap forward for the leukodystrophy community with the adoption of twelve new diagnostic definitions through the International Classification of Diseases – Tenth Revision. The ICD-10 code system is used by the health field to classify diagnoses, symptoms, and procedures for claims processing. While this system is largely used when it comes to insurance billing, it is also extremely useful for the health care system as a whole. The ICD-10 system is leveraged by physicians and researchers all over the world to track diseases, severity of progression, treatment outcomes, and more. Ultimately having these twelve new codes will result in faster diagnosis, more thorough treatment plans, and overall improved quality of life for patients currently affected and all who are diagnosed with leukodystrophies in the future.

To have twelve codes awarded at one time is simply unheard of considering how difficult it can be to obtain even one, but thanks to the unyielding dedication of Dr. Joshua Bonkowsky (University of Utah Health and Intermountain Primary Children's Hospital) and Monika Baker (University of Utah MD/PhD Student), the leukodystrophy community now enters a new era.

ICD-10-CM	Diagnosis
E75.27	Pelizaeus-Merzbacher Disease
E75.28	Canavan Disease
E79.81	Aicardi-Goutieres-Syndrome (AGS)
E79.82	Hereditary Xanthinuria
E79.89	Other Specified Disorders of Purine/Pyrimidine Metabolism
E88.43	Disorders of Mitochondrial tRNA Synthetases
G11.5	Pol III-Related Leukodystrophy (4H)
G31.80	Unspecified Leukodystrophy

ICD-10-CM	Diagnosis
G11.6	Vanishing White Matter Disease (VWM)
G23.3	TUB4A-Related Leukodystrophy (H-ABC)
G31.86	Alexander Disease
G90.B	Adult Onset Autosomal Dominant (ADLD)
G93.42	Megaloencephalic Leukoencephalopathy with Subcortical Cysts (MSL)
G93.43	Leukoencephalopathy, Cerebral Calcifications and Cysts (LCC)
G93.44	Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia (ALSP)

Now that the twelve new leukodystrophy codes are in place and can be used, it opens up a plethora of opportunities for medical professionals and patients alike. The codes are an integral part of disease awareness and ease of educational material for physicians. Doctors who have never encountered leukodystrophies before will now have real patient case studies at their fingertips. Patients will have one more resource in their toolbox when it comes to seeking out diagnostic and treatment

options. Researchers will have access to information that was previously scatered inconsistently among many ICD codes that didn't truly ever define leukodystrophies for what they are, streamlining clinical trials and other projects.

It is encouraged that all patients affected by leukodystrophies educate their care teams on the new codes, and ensure that their charts reflect the new classification. Physicians are also encouraged to educate themselves on the new codes and begin using them immediately.

The ULF wishes to congratulate Dr. Joshua Bonkowsky and Monika Baker on their amazing achievement, and congratulations to the leukodystrophy community as a whole for this historic moment in medical history!

12 NUMBERS THAT WILL CHANGE LIVES

By creating ICD codes for leukodystrophies, researchers put a dozen rare diseases on the map.

Written by and shared with permission of Julie Kiefer, University of Utah Health

Tina Holman never looks forward to bringing her daughter Savannah to a clinician they haven't seen before. She knows that, yet again, she'll need to explain her daughter's rare condition, vanishing white matter disease, and answer questions about her extensive medical history.

Her family never expected that Savannah would develop a medically complex condition. She hit childhood milestones—talking, walking, running—until age 4, when it became hard for her to stay balanced. By 6 years old, she was in a wheelchair, and at 10 her back started to curve from scoliosis until it was at an 80-degree angle. Now, at age 21, Savannah's back is fused straight. But she still needs a wheelchair, is developmentally delayed, and lacks coordination, making it hard for her to do everyday tasks. That doesn't stop her from enjoying school, where she is learning how to do laundry, cooking, cleaning, and "everything," Savannah exclaims with a smile. "Overall, she is doing really well," Tina says.

Pediatric neurologist Joshua Bonkowsky, MD, with Savannah Holman and her mother Tina.

Despite successes, a lack of readily accessible information on Savannah's disease has limited her care, according to Joshua Bonkowsky, MD, PhD, her pediatric neurologist at University of Utah Health and Intermountain Primary Children's Hospital. In collaboration with Monika Baker, an MD/PhD student at the U, they arrived at a solution that could one day benefit patients like Savannah worldwide.

In a two-year process that entailed rigorous reviews by national committees, a public comment period, and a face-to-face defense., the clinician-scientists successfully landed 12 new codes in the International Statistical Classification of Diseases and Related Health Problems 10th edition Clinical Modification (ICD-10-CM), a medical classification list maintained by the National Center for Health Statistics. Getting a single new code is considered a feat, so 12 is a phenomenon. All were for different types of leukodystrophies, diseases that are in the same class as Savannah's. "We got this done because we were stubborn," Baker says. "I hope we've been able to show a pathway for others."

Originally designed for medical billing, ICD codes are obscure outside the medical field. But scientists are increasingly recognizing their utility beyond this singular purpose. The code (G11.6 for vanishing white matter disease) acts like a library's Dewey decimal system or a social media hashtag. Searching for a disease's code pulls out data on just that disease from a sea of doctor's notes in electronic health records.

With this tool, health care providers and researchers can turn up descriptions of the range and severity of symptoms for that disease, available tests, treatments and services, how patients respond, how the disease changes over time, and much more. For health care providers, a code offers a way to learn about a disease based on information from patients worldwide, and they can use it to connect patients to treatments and clinical trials. For scientists, it provides a toehold for additional research that can eventually lead to improved care for patients. "Before, everything was a blur. Now we can focus in and see what's happening," Bonkowsky says. "It's a tool we didn't have before."

ICD-10-CM has more than 68,000 codes that include listings ranging from heart disease to blood infection to being sucked into a jet engine. The ICD committee originally was hesitant to grant so many codes for leukodystrophies. However, working with Bonkowsky and Baker, they developed 12 new codes that have the greatest potential to benefit patients. The newest listings are for some of the more common leukodystrophies and conditions with treatments that are FDA-approved or close to approval.

Case in point: Savannah is now taking part in a clinical trial. With the ICD code for vanishing white matter disease launching on October 1, the information gained from her experience has a better chance of being seen by other clinicians treating patients like her. Then, health care providers and families will be empowered to decide if that same course of action is right for them.

"It's unfortunate we had to wait so long," Bonkowsky says. "It's like the starting bell is now for these diseases."

BEYOND GAIT AND BALANCE

Characterization and Management of Urinary and Bowel Symptoms in X-linked Adrenoleukodystrophy

Summary by Sia Kermani and Alex Chapleau

While the clinical characteristics of X-linked ALD is relatively well characterized, disease manifestations outside the typical motor impairments is less understood. Gaining an understanding of urinary and bowel incontinence affecting individuals with ALD can aid in determining care plans and treatment, with the ultimate goal of increasing quality of life for these patients

Summary:

Adrenoleukodystrophy (ALD) is a type of genetic condition that is characterized by damage to the membrane (myelin sheath) that insulates nerve cells in the brain. ALD can present in different ways, two of the most common types are cerebral adrenoleukodystrophy (CALD) and adrenomyeloneuropathy (AMN), which differ mainly in age of onset and progression. AMN presents in adulthood and affects the spinal cord and peripheral nerves. It has a slower progression leading to gait and balance disturbances, sensory impairment, and bowel and bladder dysfunction. Motor and sensory symptoms such as gait and balance have been well-studied, however, less information is available on urinary and bowel dysfunction in adults with ALD. As urinary and bowel incontinence drastically affect quality of life, it is paramount to better understand how AMN affects these processes in order to provide relief and treatment. Prior to this paper, previous studies demonstrated how common urinary and fecal incontinence is in female ALD patients. However, since these studies only included research in the female sex, the prevalence and impact of these symptoms for all ALD patients remains undetermined. This current study was one of the first to systematically describe the age of onset, prevalence for urinary and bowel symptoms, symptom management, and the impact of symptoms on quality of life in this patient population, while also evaluating any sex differences in symptom presentation.

The results of this study demonstrated that urinary and bowel symptoms were common in both males and females with ALD and significantly impacted quality of life. Additionally, urinary urgency (the sudden urge to urinate) was shown to be a common early symptom, often preceding incontinence. Sex-based differences found that the onset of urinary/bowel symptoms occurred approximately a decade earlier in males and symptoms were more variable in females. Furthermore, in the majority of patients, urinary and bowel symptoms were seen to develop prior to other more typical motor symptoms (such as gait/balance impairment or muscle weakness).

In order to measure bladder function, many clinicians and researchers rely on urodynamic studies (UDS). These test how well the bladder, sphincters (muscles that work to open/close passages in the body, such as the opening of the bladder), and urethra hold and release urine. Using this method, three distinct mechanisms underlying lower urinary tract dysfunction in ALD were determined.

1. Involuntary detrusor contractions with or without urine leakage: these occur when the bladder muscle spasms or squeezes suddenly without warning, giving one the feeling of urgently needing to urinate. This can indicate uncontrolled stimulation from the nervous system.
2. Motor underactivity of the bladder during urination: in this case, the bladder muscles are not contracting as much as they should, which can impair bladder emptying. Often this results in urinary retention and/or hesitancy.
3. Asynergy between detrusor contraction and sphincter relaxation: here, the timing of the bladder muscle working to release urine and the sphincter relaxing to allow passage of the urine out of the body, is off.

*The most common of these mechanisms among patients is involuntary detrusor contractions

Previous research has demonstrated that ALD patients with impaired ambulation experience more severe urinary symptoms than patients who are still remain able to walk. This suggests patients who experience urgency and incontinence will experience more difficulty being able to reach a restroom in time. Additionally, most patients with gait difficulties and imbalance also suffer from both urinary and fecal urgency and incontinence, further compounding the poor quality of life.

It has been suggested that UDS can be used to determine the mechanism of urinary dysfunction in a particular patient, rather than managing symptoms based on clinical presentation alone. Therefore, a treatment can be selected that appropriately targets the root cause of symptoms. It may be appropriate to obtain a baseline UDS in young adult patients with ALD to track changes over time, and to repeat UDS with changes in clinical presentation.

References:

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Huffnagel, I. C., van Ballegoij, W., van Geel, B. M., Vos, J., Kemp, S., & Engelen, M. (2019). Progression of myelopathy in males with adrenoleukodystrophy: towards clinical trial readiness. *Brain: a journal of neurology*, 142(2), 334–343. https://doi-org.proxy3.library.mcgill.ca/10.1093/brain/awy299

A TREATMENT FOR LATE-INFANTILE KRABBE DISEASE

Summary by Arthur Bookstein

Variants in the AARS1 gene may contribute to different disease onset and prognosis among patients with cytoplasmic transfer RNA (tRNA) synthetase-related disorders.

Summary:

Our bodies consist of many tiny building blocks called cells. Inside these cells, there are even smaller components that accomplish tasks that allow cells to function properly. One of these components, an enzyme called aminoacyl-transfer RNA synthetase (aaRS), plays an important role in the synthesis of the proteins that make up our body. tRNA synthetase is responsible for making sure the building blocks of proteins, known as amino acids, are paired with the correct type of tRNA, which is a molecular transporter.

AARS1 is a gene that encodes one of these aaRS proteins. This study focuses on the disease caused by variants in the AARS1 gene. The AARS1 gene is responsible for encoding an enzyme that plays a crucial role in protein production in our bodies. Variations in this gene have been linked to a range of neurological conditions.

The study aimed to understand the variability in the symptoms and progression of the disease caused by the AARS1 gene. The researchers conducted a cross-sectional survey on individuals with biallelic variants in AARS1, meaning they had variations in both copies of the AARS1 gene, one inherited from each parent. They reviewed clinical data, neuroimaging, and genetic testing results of these individuals.

The researchers identified 11 affected individuals and found two distinct types of disease presentations. The first type was an early infantile-onset disease, which resembled previously reported cases of AARS1-related epileptic encephalopathy with deficient myelination. This means that these patients started showing symptoms early in infancy, including seizures and problems with the formation of myelin, a protective layer that covers nerve fibers.

The second type was a later-onset disorder, where symptoms started appearing after the first year of life. This was characterized by a progressive disease affecting the white matter of the brain, which is responsible for transmitting signals in the brain. This disease started in the posterior part of the brain and gradually spread to include the frontal white matter.

The researchers also measured the activity of the enzyme produced by the AARS1 gene in available fibroblasts, a type of cell in connective tissue. They found that the enzyme activity was significantly reduced in five affected individuals, both with early infantile-onset and late-onset phenotypes.

The study concluded that variants in the AARS1 gene result in a broader clinical spectrum than previously appreciated. While the predominant form results in early infantile-onset disease with epileptic encephalopathy and deficient myelination, a subgroup of affected individuals manifests with late-onset disease and similarly rapid progressive clinical decline. The researchers suggest that longitudinal imaging and clinical follow-up will be valuable in understanding factors affecting disease progression and outcome.

This study provides valuable insights into the phenotypic variability of AARS1-related disease by highlighting the variability in disease onset and presentation. These findings suggest that genetic testing could help with early identification and management of AARS1-related disease. Further research is needed to fully understand the pathophysiology of the disease and develop effective treatments.

Sources:

Helman G, Mendes MI, Nicita F, et al. Expanded phenotype of AARS1-related white matter disease. Genet Med. 2021;23(12):2352-2359. doi:10.1038/s41436-021-01286-8

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