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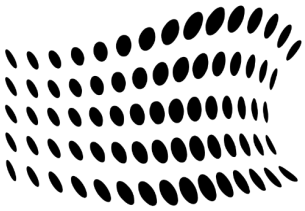

ADLD Center

Medical Disclaimer

This handbook provides general information about ADLD. The information and other content provided in this handbook is not intended and should not be construed as medical advice, nor is the information a substitute for professional medical expertise, advice, diagnosis, or treatment. **All contents found in this handbook are for reference and informational purposes only.** This handbook is not an attempt to practice medicine or provide specific medical advice, and it should not be used to make a diagnosis or to replace or overrule a qualified health care provider's judgment. Always consult with a qualified and licensed physician or other qualified healthcare provider with any questions you may have regarding a medical condition and follow their advice without delay regardless of anything read in this handbook. Never disregard professional medical advice or delay in seeking it because of something you have read here.

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Introduction

This handbook serves as a valuable resource for individuals recently diagnosed with ADLD (Autosomal Dominant Leukodystrophy). Its primary objective is to provide comprehensive support and guidance during the often-challenging period faced by patients and their families when confronted with a new diagnosis of ADLD. It is intended to serve as a stepping stone towards seeking the necessary assistance and strategically planning the subsequent steps required.

Within this guide, you will find essential information covering a range of crucial topics related to ADLD, including:

- An in-depth understanding of the fundamental aspects of ADLD.
- Exploring the potential impact of ADLD on familial dynamics.
- Discovering effective strategies and reliable resources for optimal care and management of ADLD.
- Navigating the support network available to prevent feelings of isolation and foster well-being during the ADLD journey.

Receiving a diagnosis of ADLD, whether for oneself or a loved one, undoubtedly marks a significant moment in an individual's life. Suddenly, life takes an unexpected turn, and a mix of emotions may arise. Concerns may emerge regarding the implications of this diagnosis for both the individual and their family's quality of life. Adjusting to the challenges of daily life and assuming the responsibilities of caregiving can be daunting. Moreover, it is not uncommon to be inundated with copious amounts of information. During this critical period, it is crucial to seek emotional support and accurate information that can assist in coping effectively and fostering a positive trajectory for both the individual with ADLD and their family.

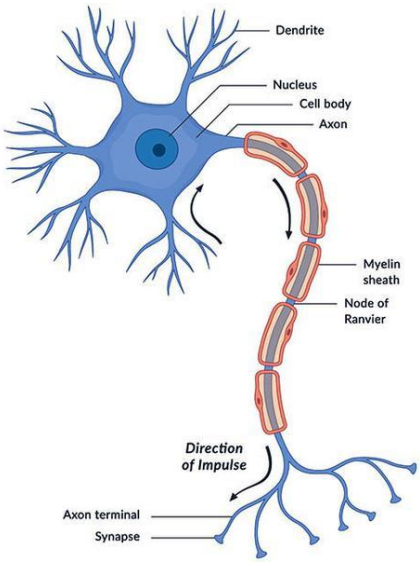
ADLD is a specific form of leukodystrophy characterized by autosomal dominant inheritance and primarily affects the white matter of the brain. While there may be similarities among leukodystrophies in terms of general aspects, it is important to recognize that each subtype, including ADLD, has distinct features and progression patterns. Therefore, it is essential to approach the acquired knowledge about ADLD with a discerning mindset. Not all information may be applicable to every individual or their family, and its relevance may evolve over time.

Please be mindful that the information provided is current to the best of our abilities. Nevertheless, research and medical understanding of ADLD continue to evolve. Consequently, updates to this resource will be made periodically to ensure the information remains relevant and accurate. As always, it is advisable to consult with your healthcare team to discuss any medical concerns or potential modifications to your medical care specific to ADLD.

Autosomal Dominant Leukodystrophy

What is ADLD?

Autosomal dominant leukodystrophy (ADLD) is a disorder of the central nervous system (i.e., the brain and spinal cord) in which myelin, a special coating on nerves, gets damaged over time.



ADLD typically presents in adults around ages 40 to 60. Symptoms worsen over time as more myelin gets damaged and more nerves get affected.
ADLD first affects what is called the autonomic nervous system, which regulates involuntary bodily responses such as body temperature and blood pressure. This results in symptoms such as:

- Frequent urination
- Constipation
- Feeling light-headed when standing due to sudden drops in blood pressure
- Erectile dysfunction

Symptoms typically start in the legs and later move to the arms and then to the facial muscles. Later on during the course of the disease, voluntary movements get affected. This can result in symptoms such as:

- Stiff or weak muscles
- Muscle shaking that worsens with movement (called intention tremor)
- Difficulty with coordination (called ataxia)
- Difficulty walking

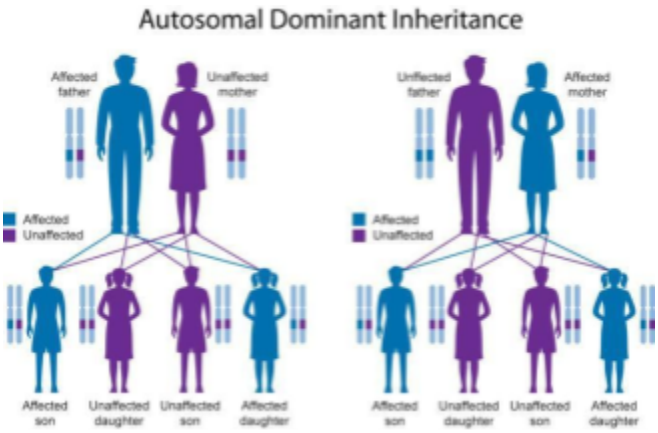
How common is ADLD?

ADLD is rare, with at least 100 documented patients reported in the literature from around the world, including the Americas, Europe, and Asia. Having said that, ADLD is thought to be underdiagnosed due to limited ability to diagnose it in areas without access to specialists and genetic tests.

What causes ADLD?

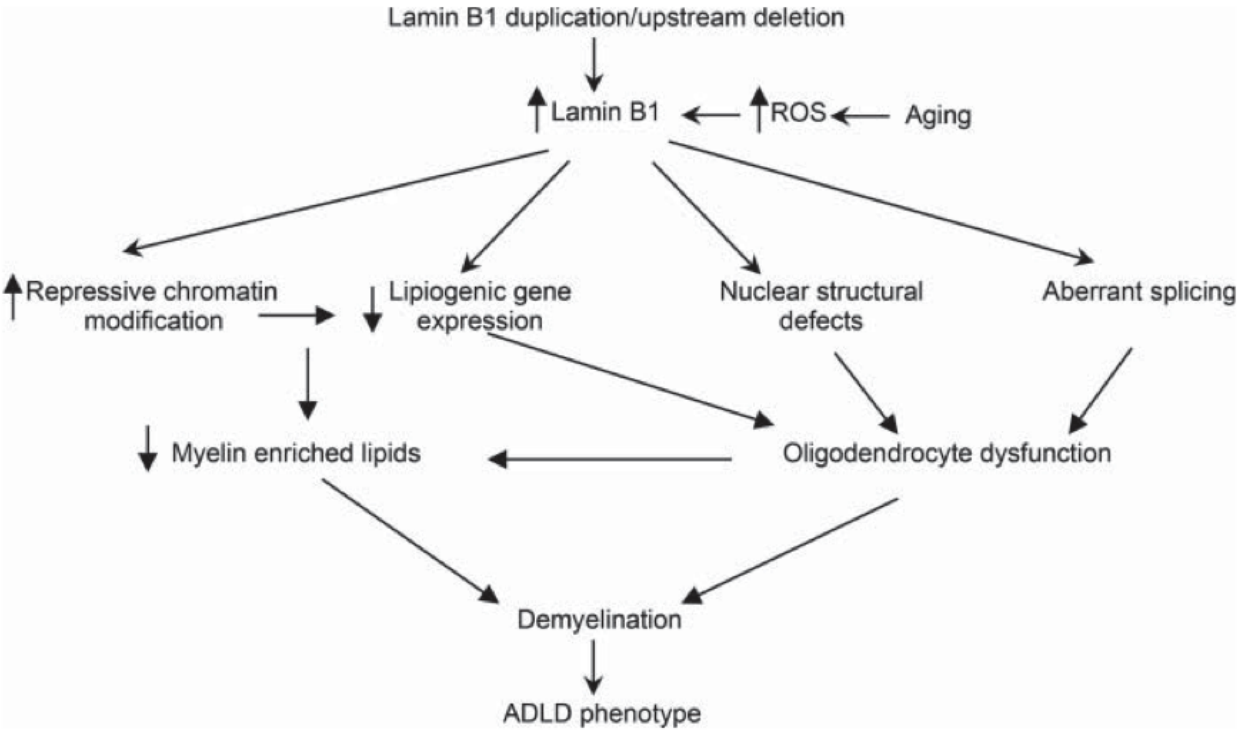
ADLD is an autosomal dominant genetic disorder, which means someone who has ADLD has a 50% chance of passing it on to each of their children. Typically, someone who has ADLD also has an affected parent.

ADLD is caused by mutations in a gene called LMNB1. This gene gives your body instructions on how to create a protein called LaminB1. LaminB1 is an important part of every cell in your



An autosomal dominant inheritance chart shows the transmission of a trait or disorder from generation to generation, where only one mutated copy of the gene is sufficient for an individual to be affected and there is 50% chance of an affected parent transmitting the mutation to their offspring of either sex.

body. It is involved in providing structure to the shell around the nucleus, which is inside each of your cells. Having too much Lamin B1 can reduce the activity of genes responsible for making fats and important fats for nerve insulation (myelin). This happens through certain ways that are influenced by a person's age. This model helps us understand how these changes in gene activity can explain some of the differences in the disease depending on a person's age and the specific cells affected. There are other factors, like how the body responds to stress, changes in the shape of the nucleus, and alterations in how genetic information is processed, that may also play



a role in the disease. These factors can work together or separately to contribute to the symptoms and characteristics of ADLD.

Is ADLD the same as MS?

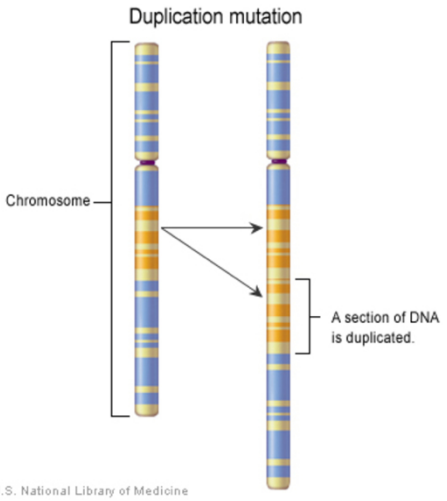
No. Another common disorder that affects myelin is multiple sclerosis (MS). Sometimes, ADLD patients get misdiagnosed as having MS. However, ADLD differs from MS in its symptoms as well as its root cause. ADLD is caused by a mutation in the LMNB1 gene. It is unknown which genes are responsible for MS. Furthermore, MS is not directly genetically inherited. In addition,

symptoms of ADLD don't typically present until patients are around 40 to 60 years old, while MS patients typically start noticing symptoms between ages 20 and 40.

How is ADLD diagnosed?

Abnormal MRI results can prompt genetic testing, which allows for definitive diagnosis.
Getting tested for ADLD involves giving a saliva sample or blood, which is sent to a lab for genetic analysis.

For context on how genetic testing works, each of the cells in your body contains DNA, or genetic material, that is made up of a series of nucleotides. The 4 nucleotides are known as A,C,T, and G. When you send in a sample for genetic testing, the lab looks at the order of these nucleotides to see if there are any misspellings of your DNA that might be causing the symptoms you're experiencing. Most genetic disorders can be found through this "spell-check"-like method. ADLD (Autosomal Dominant Leukodystrophy) can occur due to specific duplication or deletion events in the LMNB1 gene:



- Duplication of LMNB1 gene: In some cases of ADLD, there can be a duplication (extra copy) of the LMNB1 gene. This means that instead of having the usual two copies of the gene, affected individuals have three copies. This duplication leads to an overproduction of the LaminB1 protein, which can disrupt normal cellular processes and contribute to the development of ADLD symptoms.

- Deletion of LMNB1 gene: Deletion (upstream of LMNB1): In this scenario, the LMNB1 gene and the instructions it gives the body to make the LaminB1 protein are "read" too much, which results in the same outcome as the duplication, which is too much LaminB1 protein getting made. This is known as the "position effect." The position effect occurs when there is a rearrangement of the order of your DNA in such a way that the LMNB1 gene is "turned on" too often, which causes overproduction of LaminB1. The deletion is a rarer cause of ADLD than the duplication.

Both duplication and deletion events in the LMNB1 gene can lead to abnormal levels of LaminB1 protein, affecting the structure and function of cells, particularly those involved in the formation and maintenance of myelin, the protective covering of nerve fibers. These disruptions in myelin can cause the characteristic symptoms of ADLD, such as progressive neurological impairments and white matter abnormalities in the brain.

Since ADLD is not caused by a misspelling of DNA and is instead caused by either an extra copy of the LMNB1 gene or a deletion upstream of it, it can be difficult for some labs to find

during genetic testing. Therefore, it's important to send your DNA sample to a lab which has been confirmed to be able to detect ADLD.

- Within the US, the only lab that accurately tests for ADLD is Nemours Lab in Delaware. You can get in contact with Dr. Grace Hobson to schedule an appointment to get a test here.
- Internationally, Centogene offers testing, but they are only able to detect some cases of ADLD.

If I want to have children, can I prevent passing on ADLD to them?

Yes, you could explore pre-implantation genetic testing of embryos — Some couples may find that they are carriers of a disease-specific gene or a known genetic mutation that could be passed on to their children. In these situations, couples may choose to have their embryos tested prior to transfer to find out which of the embryos have the disease or genetic mutation, and then transfer only those which do not.

Patients should be aware that, while helpful in certain situations, pre-implantation testing is not perfect, and women who get pregnant after such testing still need to have standard prenatal testing. Please talk to your OB/Gyn to learn more about other risks associated with embryo testing.

Getting Care

Finding a provider

It's important to get in touch with a local neurologist who you trust to help manage your primary care with the disorder. The ADLD Center team is working on establishing a clinical care network made up of physicians with relevant expertise and experience working with ADLD patients. Some options are as follows:

- Mayo Clinic
- University of Pittsburgh – Medical Center
- Massachusetts General Hospital
- University of Bologna
- University of California – San Francisco
- University of California – Los Angeles
- Faculté de Médecine, Université Laval

We are aware of physicians who have treated ADLD patients at the above locations. Please email us at contact@adld.center if you would like to be connected with your nearest clinical center.

Assembling your medical team

When assembling your team, talk to your doctor about connecting with the following specialists:

- Leukodystrophy Neurologist
- Urologist or Neuro-Urologist
- Center for Sleep Medicine
- Medical Geneticist
- Occupational Therapist
- Physical Therapist
- Neuro-Psychiatrist
- Physical Medicine and Rehabilitation (PM&R)
- Radiology for MRI
- Pulmonary Medicine
- Laboratory Medicine and Pathology

Symptom Management & Treatment

Some medical treatments for ADLD symptom management that you can talk to your doctor about:

- Muscle relaxants such as benzodiazepines and baclofen
- Clonazepam, Sinemet, and Artane could be tried for cerebellar symptoms
- Detrol or Ditropan for bladder overactivity
- Possible antiarrhythmics or pacemakers for cardiac rhythm disturbance
- Selective serotonin reuptake inhibitors for symptoms of depression

There is no cure for ADLD at this time. While we cannot reverse the damage caused by the disease once the symptoms have begun, there are medicines available for symptom management, which can improve your quality of life. These include medicines for:

- Urinary tract health and treatment for urinary tract infection
- Laxatives and dietary fiber for constipation
- Speech therapy
- Feeding interventions, like softened foods or tube-feeding
- Physical therapy
- Occupational therapy
- Walking aids, such as walkers or wheelchairs

ADLD symptoms worsen over time and people usually live with symptoms for 10-20 years before complications can lead to fatality. Later symptoms of ADLD include:

- Loss of ability to walk or move
- Difficulty speaking
- Difficulty swallowing
- Involuntary laughing or crying
- Cognitive impairment, including dementia

Diet, Nutrition & Other

Some holistic approaches to symptom management include:

- **Exercise safely.** Speak to a doctor about safe ways to keep your blood flowing. Whether it's walking in a pool or doing body weight exercises, your local physical rehab center may be able to help provide you with the equipment and support needed.
    - **Stand up slowly.** This is critical for those with autonomic dysfunction who may feel lightheaded when suddenly sitting or standing.
    - **Stretch daily.** This helps with preventing muscle spasms and weakness as well as treating them in the moment.
- **Consider your diet.** Drink plenty of water, eat vegetables and introduce healthy probiotics into your diet. A healthy diet cannot be overstated for overall energy and digestion. Find what works for you.
- **Use a shower chair.** Falls can happen, but preventing them where possible is key for ADLD patients as head trauma can worsen the condition. And frankly, bathrooms are a dangerous place for anyone at any age. So treat yourself to a shower chair to avoid unnecessary slips and, please, if help is available, accept it when transferring in and out. We can all use a hand!
- **Add a waffle-cushion or ROHO Mosaic.** A critical item, these cushions not only go a long way in preventing bed sores, but they also make for a more comfortable seat. Get multiple and keep one everywhere you sit: on your car seat, your zero gravity chair, wheel chair etc. It is much easier to prevent a bed sore than to treat it.
- **Consider an alternating air pressure mattress.** This $70 mattress pad fits snugly under the sheets to increase comfort for those unable to adjust or move as easily in bed, and it actively prevents/treats bed sores. There's no need to spend a fortune or purchase a whole new bed, and the benefits cannot be overstated Make sure to adjust the

pressure dial based on your body weight. Lighter people may need less pressure, whereas heavier folks may benefit from stronger pressure. Do some research to be sure which setting is best for you.

- **Adjustable mattress.** This allows you to adjust your mattress to a variety of positions. This is especially helpful during extended periods in bed, and also allows the mattress to be adjusted to an upright position, which can be helpful when eating and/or drinking.
- **Explore low/no-alcoholic beverages.** It doesn't seem fair that a single drink can exacerbate symptoms. But there are some excellent beverages out there these days that allow you to still take part in the fun. Ariel is a good alcohol free wine. Sometimes a glass of pomegranate juice or a good mocktail can do the trick too!
- **Use PVA towels.** Keep these on hand for $9. Store in the fridge or freezer and use when you need to cool down quickly to regain energy.
- Some additional approaches that could work include supplements (specifically Vitamin D and B12), acupuncture, acupressure/massage therapy, homeopathy, and ayurveda.

It's important to begin therapies such as speech, physical, and occupational therapy early in order to gain the most benefit from them.

Gyrostim is a neurotechnology that uses fast rotating motion to provide mild stimuli to the vestibular and proprioceptive systems, which has applications in neurologic rehabilitation and balance/motion disorders.

Can I be denied insurance coverage due to positive genetic test results?

In the USA, genetic information is protected by a law called GINA (Genetic Information Nondiscrimination Act), which prevents discrimination by employers and health insurance companies in most cases (exceptions include the military, federal government, and employers with less than 15 employees). However, GINA does not protect from discrimination by life insurance, disability insurance, and long-term care insurance companies that can use your genetic information to make policy decisions. GINA does not apply for individuals who already have symptoms. To learn more, visit www.GINAhelp.org.

We recommend putting insurance in place prior to getting genetically tested for ADLD.

Resources:

While this is a difficult disorder, you are not alone.

- https://adld.center/
    - Register for the patient registry and sign up to receive a quarterly newsletter sharing recent scientific advances and interviews with patients.
- The united leukodystrophy foundation: https://ulf.org/
    - Find events, and online support groups here.
- https://unitedbrainassociation.org/brain-resources/autosomal-dominant-lukodystrophy-adld/
    - Sign up to get news and share your story.

- https://www.huntershope.org/adld/
- https://medlineplus.gov/genetics/condition/autosomal-dominant-leukodystrophy-with-autonomic-disease/#synonyms
- In addition, as we know this is a genetic disorder, there is a risk of inheritance within the family. Anyone wanting to assess their risk of ADLD should consult with a genetic counselor, which is a trained medical professional who specializes in genetic conditions and can help you make informed decisions about genetic testing and inherited risks. You can find a genetic counselor near you through https://findageneticcounselor.nsgc.org/.

Managing Mental Health

Tips for managing your mental health:

- Start with a self-screening. Taking an online mental health screening, such as Mental Health America's mental health tests, can be a first step in reflecting on one's feelings before talking to their health care provider or a mental health specialist.
- Talk to a professional. It is important for ADLD patients to utilize their health care provider for information on physical and emotional health. They may be able to help with certain mental health issues and can provide a reference to a counselor or other support services.
- Ask for help. Family members and friends can serve as a great support system. ADLD patients are encouraged to ask for help when they need it.
- Join a support group. Talking to others who have had similar experiences can be therapeutic. Rare disease patients may be able to find in-person and virtual support groups through hospitals as well as rare disease support organizations.
    - Global Genes (globalgenes.org) is an organization that provides information to those affected by rare diseases in general and ANGEL AID (angelaidcares.org) provides a variety of mental health and wellness services to rare disease families including rare mothers' wellness retreats and online support groups facilitated by professional psychologists or therapists.
- Live in the present. Finding ways to feel grounded and focused on the present moment can help to avoid feelings of worry about future events and outcomes. Prayer and spiritual practices are helpful to some patients. Other options include meditation and mindfulness exercises.
- Keep a journal. It can be hard to remember feelings from a week ago, let alone the entire span of treatment. Tracking one's emotions on a daily basis can serve as a reminder for an individual to reflect on how they are feeling and aid in monitoring symptoms of mental health issues.
- Make time for exercise. While the ability to participate in different levels of physical activity may vary depending on one's treatment regimen and diagnosis, exercise can play a helpful role in managing mental health. Even light walking can help with feelings of anxiety and depression.

Clinical Research

Path to Clinical Trial

The ADLD Center is engaged in various spheres of research with the aim of developing a treatment/cure for this challenging disease. The following efforts are ongoing and showing promising signs:

- Academic Research: The ADLD Center has funded 4 research grants over the past year with an aim to develop gene silencing therapies and biomarkers
- Translational Research: Various efforts are ongoing in order to ensure clinical trial readiness as the drug screening process nears a pivotal checkpoint in 2024

Patient Registries and Natural History Studies

Once the development of a therapy or cure for ADLD has advanced far enough to start a clinical trial, it will be essential to have as much clinical data as possible from all ADLD patients. This will allow for quick identification of eligible patients as well as discovery of quantifiable clinical outcome measures, or in other words, metrics based upon which physicians will know if the treatment or cure is working. Without quantifiable clinical outcome measures, improvement in patient condition cannot be measured, which causes a trial to be postponed until this data is available.

A natural history study is a type of clinical study that observes the course of a disease over time in the absence of medical intervention or treatment. Natural history studies play an important role in medicine for several reasons:

- They provide vital information about how a disease normally progresses from onset to advanced stages. This includes details on symptoms, biomarkers, disability, decline in function, and survival.
- They establish baselines or benchmarks about the untreated natural course of the disease that can inform the design of future clinical trials of new treatments.
- They identify clinically relevant endpoints, optimal patient populations, expected event rates, and appropriate observation periods to incorporate into trial designs.
- They allow comparisons of the effectiveness of new treatments to the natural history benchmarks. Interventions that significantly improve upon the natural course indicate effectiveness.
- They can provide insights into disease mechanisms, risk factors, and prognostic indicators associated with progression.
- For very rare diseases, natural history studies may be the only way to systematically gather data and understand the disease patterns.

In summary, natural history studies advance our understanding of disease pathogenesis and trajectories which facilitates better clinical trial design and evaluation of emerging therapies for treatment. They provide the foundation for successful drug development programs, especially for novel therapies for rare diseases. However, they are not the same as a patient registry.

Parameter	Patient Registry	Natural History Study
Objective	Track real-world outcomes of patients over time	Understand disease progression and outcomes in absence of treatment
Example	Demyelinating Disease Registry	Natural History Study of Leukodystrophy Patients
Data Collected	Broad - demographics, diagnosis, treatments, clinical assessments	Focused on disease progression - biomarkers, imaging, functional scores
Timeline	Long-term, ongoing	Defined study period
Participants	All eligible volunteers	Defined inclusion/exclusion criteria
Interventions	Reflects real-world standard of care	No interventions, observes underlying disease course
Use of Data	Analyze usage patterns, compare treatments, recruit for trials	Establish baseline metrics for future trial design

We are in the process of setting up a Natural History Study with one of our clinical partners. In its initial stages, this will be a valuable resource for insights into disease characteristics such as symptoms, progress, and prognosis. It will also demonstrate to pharmaceutical companies that there is sufficient centralized demand to justify their investment towards manufacturing a drug.

Over time, it will function as a centralized resource that is vital to helping researchers learn more about ADLD, accelerating the development of new research and treatments, identifying issues that require additional research, and improving the care of all patients who are affected by ADLD.

The Patient Registry and Natural History Study will comply with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule to safeguard all patients´ information.

Current research and clinical trials

Please visit https://adld.center/ for a summary of the latest publications and news on ADLD.

Brain Donation

Post-mortem brain donation provides researchers with invaluable tissue samples to help uncover new insights into leukodystrophy pathology and progression. In the past, we have partnered with the Michigan Brain Bank and UPMC to coordinate brain donations from ADLD patients who voluntarily choose to contribute in this manner. The process involves signing up for a donor registry and providing consent (this can also be done by the next of kin after passing). Upon passing, the brain tissue is collected within a limited time window and stored via a rapid

cooling process to preserve tissue integrity. Samples are then distributed to research teams focused on ADLD and related leukodystrophies to enable extensive histopathological, genetic, and molecular analyses. Brain donations have been absolutely crucial for major research advances in unlocking mechanisms and pathology surrounding neurodegenerative disease, and will serve as a similarly impactful resource for ADLD. We remain sincerely grateful to our community members who make this profound contribution to accelerating ADLD research. Please reach out for any information on how to register as a prospective brain tissue donor.

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