Potential Treatment Modalities:

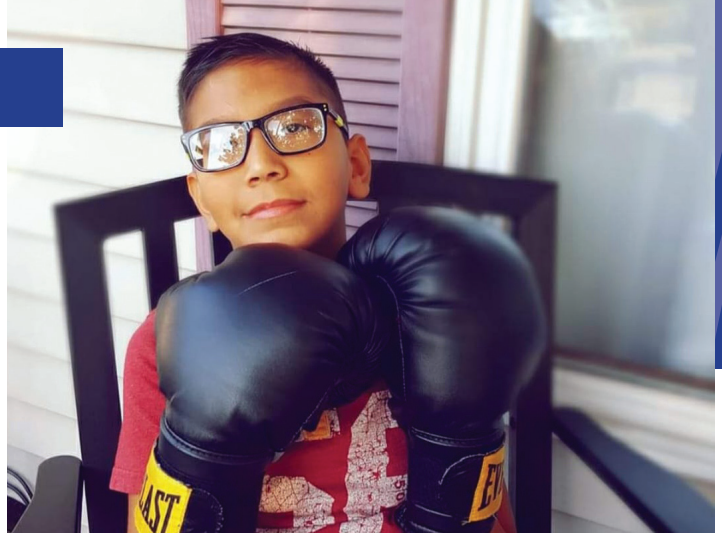
Supportive care is the primary treatment approach for the majority of leukodystrophies; nevertheless, a specific subset of leukodystrophy types benefit from approved treatments. Early intervention in these cases is critical to improve outcomes, highlighting the urgency for prompt and accurate diagnosis.

Potential Treatment Modalities for Selected Disorders:

- Hematopoietic Stem Cell Transplantation
- Gene Therapy
- Small Molecule Therapies
- Anti-sense Oligonucleotides
- Enzyme Replacement Therapy

Many of these treatments are still in the investigational phase. Please see **clinicaltrials.gov** for a current listing.

The above listed treatments typically do not reverse symptoms but may halt or significantly slow disease progression and therefore require early diagnosis before significant symptoms occur. Most leukodystrophies do not have a specific treatment or cure but there are many treatments available to help with the symptoms of the disease.



This brochure was produced by the **United Leukodystrophy Foundation** as a part of the **Patient Advocacy Group Collaboration program**.

The ULF is proud to partner with the many other leukodystrophy organizations that represent the leukodystrophy community. The ULF is happy to answer your general leukodystrophy questions and point you towards type-specific organizations or other resources when needed.

Type specific information and patient advocacy/ support groups can be found on the ULF website via the link below.

ULF.org
815-748-3211
office@ulf.org

united LEUKODYSTROPHY FOUNDATION

Meet a Neurodegenerative Zebra:

Leukodystrophy

"Leukodystrophies are heritable disorders affecting the white matter of the central nervous system with or without peripheral nervous system involvement. These disorders have in common glial cell or myelin sheath abnormalities. (1)" Leukodystrophies can be classified as hypomyelinating or non-hypomyelinating (commonly known as demyelinating) based on whether the primary defect is lack of myelin deposition during development or altered myelin homeostasis, respectively.

- Approximately 1 in 4,733 people are affected by leukodystrophy. (2)
- There are over 50 identified types of leukodystrophies.
- Approximately 20-30% of patients affected by leukodystrophy do not have a molecular diagnosis. (2)

A list of the identified leukodystrophies can be found here:

(1) M. van der Knaap, Molecular Genetics and Metabolism 2015; 114, 494-500
(2) J. Bonkowsky, Pediatric Neurology 2020; 111, 66-9

Leukodystrophy Fast Facts:

Leukodystrophies are diagnosed via MRI pattern recognition together with molecular genetic sequencing. They can be inherited in an autosomal recessive (e.g., biallelic pathogenic variants in numerous genes such as POLR3A, POLR3B, POLR1C, GALC, ARSA), dominant or *de novo* (e.g., Alexander's disease) and X-linked fashion (e.g., ABCD1, PLP1). A wide variety of cellular processes can be involved in disease pathogenesis, including lysosomal enzyme defects (e.g., metachromatic leukodystrophy, Krabbe), peroxisomal defects (e.g., adrenoleukodystrophy), mitochondrial defects, and transcription and translation defects (e.g., POLR3-related or 4H leukodystrophy), to name a few.

In general, most common symptoms will vary by age of disease onset:

Infant: Developmental delay or regression, typically motor, with or without other symptoms such as irritability and nystagmus; could be misidentified as cerebral palsy, colic, or reflux.

Childhood: problems with attention/concentration, behavioral changes, progressive motor symptoms such as gait, ataxia, tremor, and coordination difficulties; could be misidentified as ADHD, Autism, Guillain-Barré or other neuroimmune inflammatory diseases.

Adulthood: neuropsychiatric symptoms with typically milder motor involvement (e.g., spastic gait, ataxia); could be misidentified as Multiple Sclerosis, Hereditary Spastic Paraperesis (HSP) or Ataxia with or without psychiatric diseases or dementing illnesses, or brain tumors.

In all ages, brain MRI shows white matter changes.

Suggested Confirmation Strategies:

- **Brain MRI** with and without contrast
- **Genetic Testing:** Chromosome microarray, leukodystrophy panel or whole exome/genome with mtDNA sequencing and deletion/duplication analysis
- **Metabolic Testing:** lactate, ammonia, plasma amino acids, urine organic acids, very long chain fatty acids, acylcarnitine profile, carnitine profile, urine glycosaminoglycans, urine oligosaccharides, urine sulfatides, urine sialic acid, purine and pyrimidines, sterols, CDG transferrin/transferrin isoelectric focusing, lysosomal enzymes, etc.
- **Other evaluations:** EMG NCV, EEG, ophthalmology and audiology evaluations.

Distinguishing leukodystrophies from other neurodegenerative disorders may be challenging. The brain MRI and ancillary tests are usually helpful, as well as consultation with a leukodystrophy expert.

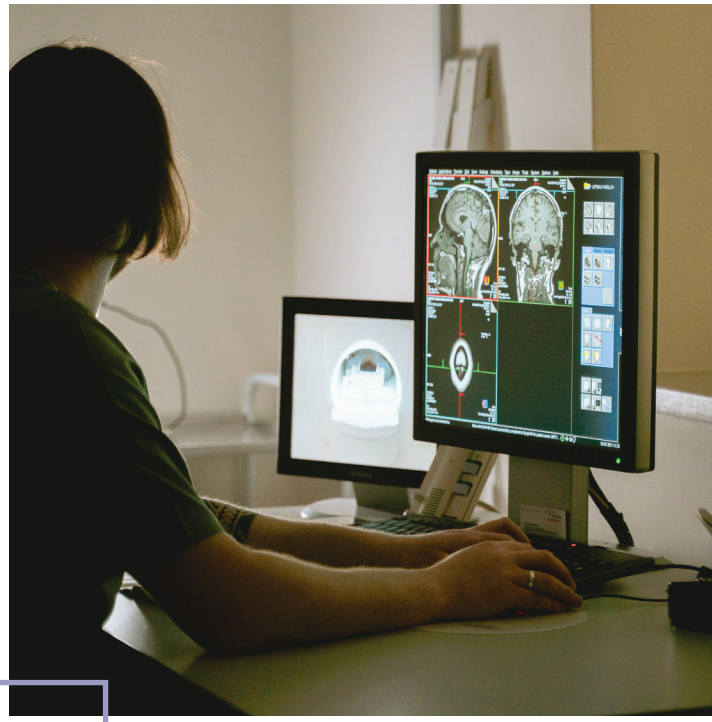
Genetic testing is crucial to differentiate a specific diagnosis from over 50 known leukodystrophies. Testing may be directed based on MRI imaging patterns and symptoms/presentation. **Please see the following articles for additional information.**

In addition, metabolic blood and urine tests maybe helpful to diagnose or confirm an inborn error of metabolism, which are frequently associated with leukodystrophies.

Newborn Screening:

Newborn Screening is key in early diagnosis and treatment prior to symptom onset.
Leukodystrophies that are currently represented in newborn screening in some countries:

- Adrenoleukodystrophy (ALD)
- Krabbe disease
- Metachromatic leukodystrophy (MLD)



Schiffmann R and van der Knaap. An MRI-based approach to the diagnosis of white matter disorders. Neurology. 2009; 72:750–759.

Parikh S, et. al.; GLIA Consortium. A clinical approach to the diagnosis of patients with leukodystrophies and genetic leukoencephelopathies. Mol Genet Metab. 2015 Apr;114(4):501-515.