

Alex TLC Research Summary

August 2025



Research summary of recent leukodystrophy research and clinical trials, includes article summaries and direct links to websites and articles.

Research summaries

[Adrenoleukodystrophy \(ALD\)](#)

Safety and efficacy of leriglitazone in childhood cerebral adrenoleukodystrophy (NEXUS): an interim analysis of an open-label, phase 2/3 trial

<https://www.sciencedirect.com/science/article/pii/S258953702500197X?via%3Dihub>

Cerebral adrenoleukodystrophy (cALD) is a rare, genetic, and life-threatening brain disorder that can affect young boys. It causes damage to the brain's white matter, leading to rapid neurological decline. The current treatment, haematopoietic stem cell transplantation (HSCT), can be effective but is high-risk, not widely available, and often delayed. While allogeneic (cells from a donor) and autologous modified (your own cells) HSCT are effective in some patients, the success is dependent on the time of transplant and the extent of cerebral disease. As a result, there is a critical need for safer, more accessible therapies. Leriglitazone is an oral drug designed to reduce inflammation, protect brain cells, and slow disease progression. In this ongoing clinical trial (NEXUS), boys aged 2–12 with early-stage cALD received daily leriglitazone for 24 weeks. The goal was to assess safety and early signs of benefit. Eleven boys were evaluated in this interim analysis and all remained clinically stable, and five (45%) showed no further disease activity on MRI scans. This suggests a possible halting of progression. Brain lesion growth slowed in all patients compared to the expected course of untreated disease. Blood tests also showed encouraging changes in key biomarkers of brain inflammation (MMP-9) and nerve damage (NfL), further supporting the drug's potential benefit. Importantly, leriglitazone was well tolerated with no serious drug-related side effects. These early results suggest that leriglitazone could offer a safer alternative or complement to HSCT, especially for children who lack timely access to transplantation. While these findings are promising, longer-term follow-up and research is needed. The full 96-week trial will determine whether leriglitazone can provide lasting protection against this devastating disease.

Cost-Effectiveness of Newborn Screening for X-Linked Adrenoleukodystrophy in the Netherlands: A Health-Economic Modelling Study

<https://www.mdpi.com/2409-515X/11/3/53>

X-linked adrenoleukodystrophy (ALD) is a rare genetic disorder that mainly affects boys. It can cause adrenal insufficiency and may result in a brain disease called childhood cerebral ALD (ccALD), which can lead to severe disability or fatality if not treated early. ALD is caused by mutations in the *ABCD1*

gene, which prevents the body from breaking down very long-chain fatty acids, leading to damage in the brain and adrenal glands. This study assessed whether adding ALD to the Dutch newborn screening (NBS) programme is cost-effective. Researchers developed a health-economic model to compare the long-term costs and health outcomes of screening versus not screening over the first 18 years of life. They found that screening costs about €2.39 per baby and around €40,630 to detect one ALD case. While screening increases healthcare costs (mostly due to regular monitoring and early treatment), it significantly improves outcomes. The cost per quality-adjusted life years (QALYs) gained was €34,084, which falls below the Dutch threshold for a cost-effective intervention (€50,000–€80,000). Although there is some uncertainty due to limited long-term data, the model shows that screening is likely cost-effective and can improve both life expectancy and quality of life. Ultimately, including ALD in newborn screening enables early diagnosis and timely treatment, potentially saving lives and supporting families. This research strongly supports expanding ALD screening as a valuable public health measure.

[Alexander Disease](#)

Diagnosing Alexander disease in adults

<https://pn.bmj.com/content/early/2025/05/10/pn-2024-004490.long>

Alexander disease (AxD) is a rare genetic disorder caused by mutations in the *GFAP* gene. It is traditionally classified into infantile, juvenile and adult forms. While early-onset cases are often severe, adult-onset AxD is very diverse in how it presents and can be mistaken for other conditions such as multiple sclerosis. In this study, researchers collected clinical and imaging data from four cases diagnosed with adult-onset AxD to provide guidance for timely referral of adult patients with suspected AxD. They found that cognitive decline was less common than in childhood forms. Common early symptoms included speech and swallowing issues, muscle stiffness and impaired balance. MRI imaging data revealed characteristic changes, including shrinkage of the brainstem and the top of the spinal cord called medulla. In the presence of suggestive clinical and neuroimaging features, genetic testing for *GFAP* mutations should be performed. Diagnosis of AxD in adults is complex and challenging, but awareness and collaboration among neurologists, neuroradiologists and medical geneticists could improve accuracy and time to diagnosis.

[Leigh syndrome](#)

Disruption of adaptive immunity does not attenuate disease in the *Ndufs4*(-/-) model of Leigh syndrome

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0324268&utm_source=email&utm_medium=email&utm_campaign=June%202025

Leigh syndrome is a severe childhood-onset brain disorder caused by mitochondrial dysfunction, when the cell's energy factories stop working properly. It leads to progressive neurological symptoms such as movement problems, muscle weakness, and breathing difficulties, often resulting in early death. Inflammation in the brain is a hallmark feature, and researchers have been investigating how the immune system contributes to the disease. This study used a well-established mouse model of Leigh syndrome (*Ndufs4* knockout mice) to test whether the adaptive immune system, which includes T cells, B cells, and natural killer (NK) cells, plays a harmful role in disease progression. Researchers

genetically removed these immune cells by deleting a gene called *Il2rg* and compared the outcomes to mice with an intact immune system. Surprisingly, removing adaptive immune cells did not improve symptoms, motor coordination, weight loss, or lifespan in the mice. This means adaptive immunity is not essential for driving the disease in this model. Previous work had shown that innate immune cells, like macrophages, do cause damage, suggesting they are the primary contributors to neuroinflammation in Leigh syndrome. These findings help focus future research on targeting innate immunity, particularly macrophages, as a more promising treatment route. While people with mitochondrial diseases often have immune issues, this study shows that not all parts of the immune system are equally involved in brain damage. In summary, the research brings us a step closer to understanding which immune pathways to target to develop more effective, safer therapies for Leigh syndrome.

Metachromatic Leukodystrophy (MLD)

Newborn Screening for Metachromatic Leukodystrophy in Tuscany: The Paradigm of a Successful Preventive Medicine Program

<https://pmc.ncbi.nlm.nih.gov/articles/PMC12101386/>

Metachromatic leukodystrophy (MLD) is a rare genetic disease characterised by the absence of the arylsulfatase A (ARSA) enzyme. This deficiency leads to the build-up of harmful substances called sulfatides. Early diagnosis is essential as the currently available treatments are only effective before symptoms appear – gene therapy (arsa-cel) for early-onset and hematopoietic stem cell transplantation (HSCT) for late-onset forms. This narrow intervention time makes MLD a candidate for newborn screening programs (NBS). In this paper, researchers in Tuscany, Italy, tested a new two-step newborn screening approach for MLD using residual dried blood spots (blood drops collected from newborn heel pricks) from routine NBS. The first test measured the levels of four types of sulfatides. If one or more were above threshold, a second test was performed on the same sample to check the activity of the ARSA enzyme. Newborns with low ARSA activity were recalled for a new DBS, and if both tests were still abnormal, further evaluation and genetic testing were offered. Between March 2023 and February 2025, 42,262 newborns were screened for MLD. Ninety (0.21%) had elevated sulfatides and underwent second-tier testing. Ten (0.02%) were recalled for either insufficient sample (n=4) or low ARSA activity (n=6). No newborns were confirmed to have MLD during this period. To validate this screening system, they tested stored newborn samples from 8 genetically confirmed MLD patients aged 2-10 years. All would have been correctly identified in the first step. They further analysed DBS from 15 non-neonatal symptomatic MLD cases (aged 2-35 years), confirming the diagnostic value of sulfatide levels. This ongoing study suggested that this two-step screening approach could reliably detect MLD. The program will continue until 80,000 newborns are screened.

Characterizing Diagnostic Delays in Metachromatic Leukodystrophy: A Real-World Data Approach

<https://pmc.ncbi.nlm.nih.gov/articles/PMC12130617/>

Metachromatic leukodystrophy (MLD) is a rare genetic disease that affects the brain. The earlier it is diagnosed, before the onset of neurological symptoms, the better the chances of successful treatment. This study examined real-world data to assess diagnostic delays and identify early clinical signs. Researchers analysed large US claims datasets and identified 174 probable MLD cases (born

after 2017) defined by using the MLD-specific International Classification of Disease (ICD-10-CM) E75.25 diagnosis code. They found that the median time between the first coded symptom and the diagnosis was 658 days, with only 8% of the cases diagnosed within the recommended window for treatment eligibility. Developmental delays, seizures, gastrointestinal and ophthalmologic concerns were commonly reported several months before diagnosis. A natural-history study on 47 early-onset MLD patients showed similar patterns, confirming the presence of early clinical features. The authors conclude that better awareness of early signs and newborn screening could help identify MLD sooner and enable timely access to the existing therapies. However, these findings rely on ICD coding without genetic confirmation, with the possibility of misclassification and under coding.

Concise Articles

[Adrenoleukodystrophy \(ALD\)](#)

Leriglitazone Marketing Authorization Application submitted for treatment of cerebral adrenoleukodystrophy has been validated by European Medicines Agency

https://www.minoryx.com/media/leriglitazone_maa_submitted_for_treatment_of_cald_has_been_validated_by_ema/

Minoryx receives a EUR 26.9m grant within the framework of the European IPCEI Med4Cure project for the continued development of leriglitazone in lethal orphan CNS diseases

https://www.minoryx.com/media/minoryx_receives_a_eur_26.9m_grant_within_the_framework_of_the_european_ipcei_med4cure_project/

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