

Alex TLC Research Summary

October 2026



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

Clinical trial updates

[Adrenoleukodystrophy \(ALD\)](#)

European Commission grants marketing authorisation for NEZGLYAL® (leriglitzone), the first pharmacological treatment approved for cerebral Adrenoleukodystrophy (cALD), a rare neurodegenerative disease

[https://www.minoryx.com/media/european-commission-grants-marketing-authorisation-for-nezglial%C2%AE-\(leriglitzone\)-the-first-pharmacological-treatment-approved-for-cerebral-adrenoleukodystrophy-\(cald\)-a-rare-neurodegenerative-disease/](https://www.minoryx.com/media/european-commission-grants-marketing-authorisation-for-nezglial%C2%AE-(leriglitzone)-the-first-pharmacological-treatment-approved-for-cerebral-adrenoleukodystrophy-(cald)-a-rare-neurodegenerative-disease/)

European Commission grants marketing authorisation for NEZGLYAL® (leriglitzone), the first pharmacological treatment approved for cerebral Adrenoleukodystrophy (cALD), a rare neurodegenerative disease. The therapy is the first approved pharmacological treatment for cALD in the European Union (EU) with approval based on results from the Phase 2/3 NEXUS1 study and additional real-world evidence from compassionate use programmes. The first European launch is expected in Germany by the end of the year, with additional launches in Europe anticipated pending completion of national reimbursement negotiations. Leriglitzone is due to be assessed by NICE early next year and Alex TLC are involved in the process as the patient voice.

Research summaries

[Adrenoleukodystrophy \(ALD\)](#)

Biomarker changes in cerebral adrenoleukodystrophy after gene therapy or allogeneic hematopoietic cell transplant

[https://www.cell.com/molecular-therapy-family/advances/fulltext/S3117-387X\(26\)00156-4](https://www.cell.com/molecular-therapy-family/advances/fulltext/S3117-387X(26)00156-4)

Cerebral adrenoleukodystrophy (cALD) is a form of a rare genetic condition in which very long-chain fatty acids (VLCFA) build up in the body. This can lead to inflammation and damage to myelin, which is the protective covering around nerve fibres in the brain. Two treatments can help slow or stop this damage: gene therapy using a patient's own genetically modified stem cells, or a stem cell transplant from a healthy donor. To better understand how these treatments compare, researchers examined 21 boys who received gene therapy and 35 who received donor stem cell transplants. They measured two blood biomarkers, which are substances that can give clues about disease activity, before treatment and one year later. C26:0-lysophosphatidylcholine (C26:0-lysoPC) reflects the buildup of a VLCFA, while neurofilament light chain (NfL) can signify injury to nerve cells. Brain scans showed

greater disease progression in the gene therapy group. After one year, C26:0-lysoPC levels and NfL levels greatly decreased following donor transplantation. C26:0-lysoPC levels decreased slightly in the gene therapy group but NfL levels increased significantly. Other published data has shown that 12 months after gene therapy, 10-20% of corrected myeloid cells (immune cells) express the *ABCD1*-encoded protein, ALDP while after Allo-HCT, 100% of cells express ALDP. These findings suggest that donor transplantation may lead to more favourable changes in these metabolic measures during the first year and measures in the gene therapy need further time to normalise. However, the study does not establish which treatment is best for every patient, and 12 months is relatively early when evaluating long-term treatment outcomes. Understanding these differences could help clinicians monitor treatment responses and improve future treatment approaches.

CSF and plasma neuro-biomarker dynamics after gene therapy for cerebral adrenoleukodystrophy

[https://www.cell.com/molecular-therapy-family/advances/fulltext/S3117-387X\(26\)00037-6](https://www.cell.com/molecular-therapy-family/advances/fulltext/S3117-387X(26)00037-6)

Cerebral adrenoleukodystrophy (CALD) is a serious, progressive condition that causes inflammation and damage to the brain's white matter, which supports communication between nerve cells. It is associated with changes in the *ABCD1* gene, leading to the accumulation of very long-chain fatty acids. Gene therapy aims to halt disease progression by correcting a patient's blood stem cells so they can produce cells that support the body's immune system. In this study, researchers investigated whether biomarkers in blood plasma and cerebrospinal fluid (CSF), the fluid surrounding the brain and spinal cord, could help monitor disease activity and treatment response. They assessed 20 potential biomarkers in boys with CALD before and for up to two years after gene therapy. The most promising findings involved two proteins associated with nervous system damage and inflammation: neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP). NfL, released into body fluids when nerve cells are damaged, showed a strong relationship with disease severity measured using magnetic resonance imaging (MRI). Two years after gene therapy, patients had a median 50% reduction in blood NfL levels. Importantly, NfL levels measured six months after treatment were associated with subsequent disease progression at 12 months. This suggests that NfL could help identify patients at greater risk of continued brain damage following treatment. These findings highlight the potential of blood-based biomarkers to complement MRI scans when monitoring CALD and assessing responses to gene therapy. Although further research is needed to validate these results in larger groups, NfL could eventually support earlier identification of patients who need closer monitoring, helping clinicians make more informed decisions about care.

Disease Outcomes in Boys with *ABCD1* Variants Identified by Newborn Screening for X-ALD

<https://www.medrxiv.org/content/10.64898/2026.06.30.26356979v1>

X-linked adrenoleukodystrophy (X-ALD) is a rare genetic disorder caused by changes in the *ABCD1* gene, leading to the buildup of very long-chain fatty acids in the body. This can affect the brain and adrenal glands, which produce essential hormones. Newborn screening can identify individuals with *ABCD1* variants before symptoms appear, although predicting who will develop disease remains challenging. In this study, researchers examined 201 boys identified through newborn screening across six centres in the United States. They wanted to see whether different *ABCD1* variants were associated with adrenal insufficiency (AI), which is when the adrenal glands cannot produce enough hormones, or cerebral ALD (cALD), which causes inflammation and damage in the brain. The variants

were classified as disease-causing, likely disease-causing, or variants of uncertain significance (VUS), whose effects on health remain unclear. Overall, 26% of boys developed AI and 8% developed cALD. Rates of adrenal insufficiency were highest among boys with disease-causing variants (54%), compared with likely disease-causing variants (16%) and VUS (11%). Researchers also found that higher levels of C26:0-lysophosphatidylcholine (C26:0-LPC), a blood marker of fatty acid accumulation, were associated with an increased risk of developing AI at an earlier age. These findings suggest that combining genetic testing with blood biomarkers could help doctors better predict disease risk and personalize monitoring. An important note is that boys with uncertain variants can still develop symptoms, which highlights the need for continued follow-up.

Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy (CADASIL)

Late-Onset Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy (CADASIL) Presenting With Abnormal MRI Findings and Migraine: A Case Report

<https://www.cureus.com/articles/524231>

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a rare inherited neurological disorder affecting the brain's small blood vessels. It is caused by changes in the *NOTCH3* gene, which can damage blood vessel walls and reduce blood flow to brain tissue. Symptoms may include migraine, strokes, transient ischaemic attacks (temporary stroke-like episodes) and progressive cognitive difficulties. CADASIL typically develops during adulthood, but diagnosis can be challenging when symptoms appear later in life. This case report describes a 60-year-old Singaporean Chinese woman investigated after intermittent migraines without aura led to an unexpected finding on magnetic resonance imaging (MRI), a scan that produces detailed pictures of the brain. She had no previous history of stroke or cognitive difficulties, and her neurological examination was normal. However, further MRI scans revealed widespread changes in the brain's white matter, including areas around the external capsules and anterior temporal lobes, as well as a small, old infarct (an area of tissue damage caused by reduced blood supply) in the corpus callosum. She later experienced a transient ischaemic attack, causing temporary slurred speech. Genetic testing confirmed a disease-causing *NOTCH3* variant associated with CADASIL, and her brother's history of dementia also raised the possibility of an inherited family risk. This case highlights that CADASIL can occur later in life without typical early symptoms. Recognising characteristic MRI changes can help clinicians identify an underlying genetic cause. Although a single case cannot establish how frequently late-onset CADASIL occurs, it demonstrates the value of combining clinical assessment, brain imaging and genetic testing. Accurate diagnosis supports appropriate management, genetic counselling and family screening, helping relatives understand their potential inherited risk and improving recognition of this rare condition.

GM2 Gangliosidosis

Sandhoff Disease Associated With Bipolar Disorder: A Case Report From the United Arab Emirates

<https://www.cureus.com/articles/530138>

Sandhoff disease is a rare genetic disorder caused by changes in the *HEXB* gene that prevents certain fatty substances from being broken down properly. Their buildup in nerve cells can gradually affect movement, coordination, and sometimes mental health. Symptoms in later-onset forms can appear like other neurological or psychiatric conditions, which makes diagnosis challenging. In this case report, researchers described a 38-year-old woman living in the United Arab Emirates with Sandhoff disease and bipolar I disorder, a condition that involves episodes of unusually elevated mood or energy (mania) and sometimes depression. Her movement difficulties began in childhood and progressed to muscle weakness, speech problems, and eventually wheelchair dependence. She also experienced repeated manic episodes, including psychosis, which can make it difficult to distinguish what is real. Genetic testing confirmed Sandhoff disease, while brain imaging showed shrinkage of a part of the brain that helps control balance and coordination, known as the cerebellum. During a hospital stay, she received risperidone, lorazepam, and sodium valproate to manage her psychiatric symptoms, which improved within six days. Although she later experienced depressive symptoms, her family reported psychiatric stability at a follow-up after a period of rehabilitation and physiotherapy. This case highlights why doctors should consider genetic and neurological conditions when psychiatric symptoms occur alongside worsening physical difficulties. Although a single case cannot show whether Sandhoff disease caused her bipolar symptoms, recognising both types of symptoms may help support an earlier diagnosis and better care.

Metachromatic Leukodystrophy (MLD)

Evidence Regarding Metachromatic Leukodystrophy Newborn Screening

<https://publications.aap.org/pediatrics/article/158/Supplement%202/e2026077357E/208745/>

Metachromatic leukodystrophy (MLD) is a rare, inherited metabolic disorder affecting approximately one in 100,000 newborns. It results from changes in both copies of the *ARSA* gene, which reduce the activity of an enzyme needed to break down fatty substances called sulfatides. These substances accumulate in the nervous system, damaging myelin, the protective coating around nerve fibres. This process, known as demyelination, can cause progressive neurological deterioration, including difficulties with movement, swallowing and vision. This article reviews the evidence supporting newborn screening for MLD, focusing on early-onset forms that can progress rapidly during childhood. Without screening, diagnosis often occurs after symptoms develop, when significant and potentially irreversible damage may already have occurred. Importantly, gene therapy delivered during infancy can improve survival and motor function, making early diagnosis particularly valuable. The proposed screening approach uses a two-step process. First, a dried blood spot collected from a newborn is tested for elevated sulfatides. If levels are raised, a second test measures arylsulfatase A (*ARSA*) enzyme activity. Research suggests this approach can identify early-onset MLD accurately, with a low rate of false-positive results. However, screening is not designed to identify every form of MLD, particularly later-onset types. Pilot screening programmes are underway in the United States, while population-based programmes operate in parts of Europe. New York and Pennsylvania in the US and Norway have MLD on their NBS programs as do parts of Germany. Hannover, Germany, has reported identifying affected infants through newborn screening, enabling timely access to treatment. Overall, the evidence supports the potential benefits of introducing MLD newborn screening. Earlier detection could provide families with timely diagnoses and access to treatment before symptoms emerge. Further implementation and evaluation will help establish how screening can best improve outcomes for children affected by this devastating condition.

Please be aware these summaries are produced voluntarily by Biomedical Science students and are their interpretations of the information and findings. This information is reviewed by our Research Analyst Kristina Backlund MMSc. The National Lottery Community Fund and Ionis Pharmaceuticals, Inc have contributed to the funding of the Research Analyst role.

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