Pharmacology and Therapeutics 285 (2026) 109070

Contents lists available at ScienceDirect

Pharmacology and Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

C26:0-lysophosphatidylcholine in X-linked adrenoleukodystrophy

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ARTICLE INFO

Keywords:
Lysophosphatidylcholine
Lipidomics
Newborn screening
Biomarker
Disease severity
Prognosis
Therapeutics

ABSTRACT

X-linked adrenoleukodystrophy (ALD) is a progressive neurometabolic disorder caused by pathogenic variants in the *ABCD1* gene, resulting in the systemic accumulation of very-long-chain fatty acids (VLCFAs). C26:0-lysophosphatidylcholine (LPC(26:0)) is the primary biochemical marker of ALD and the basis for newborn screening programs worldwide. LPC(26:0) arises from the accumulation of VLCFA-CoA species that are incorporated into phosphatidylcholine via the lysophospholipid acyltransferase LPLAT10, followed by phospholipase A2-mediated hydrolysis. Compared to conventional plasma VLCFA analysis, measurement of LPC(26:0) by liquid chromatography or flow injection tandem mass spectrometry in plasma or dried blood spots offers superior sensitivity and specificity, even in female patients, for whom VLCFA analysis yields false-negative results in 15–20% of cases. Beyond diagnosis, accumulating evidence indicates that LPC(26:0) and the broader landscape of VLCFA-containing lipids correlate with disease severity. Higher levels are associated with cerebral ALD, adrenal insufficiency, and severe spinal cord disease, and data from newborn screening cohorts suggest that neonatal LPC(26:0) levels may also stratify risk for early-onset disease manifestations. LPC(26:0) accumulates in CNS lipoproteins and exhibits direct neurotoxic and proinflammatory properties in experimental models. This implicates LPC(26:0) not only as a biomarker, but also as a potential mediator of ALD pathology. Furthermore, LPC(26:0) shows promise as a pharmacodynamic biomarker of biochemical correction across therapeutic strategies, from hematopoietic stem cell transplantation to emerging approaches including ELOVL1 inhibition. However, key questions remain regarding the cell type and tissue origin of circulating LPC(26:0), its precise contribution to neuroinflammation, and the threshold levels that reliably predict clinical outcomes in individual patients.

List of abbreviations

ABC	ATP-binding cassette
ABCD1	ATP-binding cassette transporter D1
ACBD5	acyl-CoA binding domain containing prote 5
ACOX1	acyl-CoA oxidase 1
ALD	X-linked adrenoleukodystrophy
CADDS	contiguous ABCD1/DXS1357E deletion syndrome
CALD	cerebral adrenoleukodystrophy
CNS	central nervous system
CoA	coenzyme A
DBS	dried blood spot
ELOVL1	elongation of very long-chain fatty acids protein 1
ER	endoplasmic reticulum
FIA-MS/MS	flow injection analysis tandem mass spectrometry
GC	gas chromatography
HCT	hematopoietic stem cell transplantation
HDL	high-density lipoprotein
HSD17B4	D-bifunctional protein
ICAM-1	intercellular adhesion molecule 1
LCAT	lecithin:cholesterol acyltransferase
LC-MS/MS	liquid chromatography tandem mass spectrometry
LIPG	endothelial lipase
LPC	lysophosphatidylcholine
LPC(26:0)	C26:0-lysophosphatidylcholine
LPCAT	lysophosphatidylcholine acyltransferase
LPE	lysophosphatidylethanolamine
LPLAT	lysophospholipid acyltransferase

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https://doi.org/10.1016/j.pharmthera.2026.109070

Available online 19 June 2026

(*continued*)

LPLAT10	lysophospholipid acyltransferase 10
MFGE8	milk fat globule-epidermal growth factor 8
MFSD2A	major facilitator superfamily domain-containing protein 2 A
MS/MS	tandem mass spectrometry
NBS	newborn screening
NF-κB	nuclear factor kappa B
NAWM	normal-appearing white matter
PC	phosphatidylcholine
PEX	peroxin gene
PLA2	phospholipase A2
qMRI	quantitative magnetic resonance imaging
ROS	reactive oxygen species
RUSP	Recommended Uniform Screening Panel
SCD1	stearoyl-CoA desaturase-1
TG	triglyceride
TLR2/4	Toll-like receptor 2/4
VLCFA	very-long-chain fatty acid
VUS	variant of uncertain significance

1. Introduction

X-linked adrenoleukodystrophy (ALD; OMIM: 300100), the most common peroxisomal disorder, is caused by pathogenic variants in the *ABCD1* gene (Mallack et al., 2022; Mosser et al., 1993). The *ABCD1* gene encodes the ABCD1 protein, which is an ATP-binding cassette (ABC) transporter located in the peroxisomal membrane. The ABCD1 protein imports very-long-chain fatty acyl-CoA esters (VLCFA; ≥C22:0) for β-oxidation (Ofman et al., 2010; Singh et al., 1981). Loss of ABCD1 protein function impairs peroxisomal β-oxidation, resulting in the systemic accumulation of VLCFAs in plasma and tissues (A. B. Moser et al., 1999).

ALD has an estimated prevalence of 1 in 15.000–17.000 births (Bezman and Moser, 1998; A. B. Moser et al., 2016). ALD patients are asymptomatic at birth, but symptoms develop progressively. All males eventually develop spinal cord disease and peripheral neuropathy with variable onset in the third or fourth decade. Adrenocortical insufficiency occurs in approximately 80% of affected males, half of whom become symptomatic before the age of 10 (Huffnagel et al., 2019b). Adrenocortical insufficiency can be effectively managed with corticosteroid replacement therapy (Regelmann et al., 2018). Male patients have a 60% lifetime risk of developing cerebral ALD (CALD), a rapidly progressive leukodystrophy (Liberato et al., 2019). Up to 40% of cases present between the ages of 3 and 18. If left untreated, CALD can progress rapidly, leading to severe disability or death within two years of onset (H. W. Moser et al., 2001). Hematopoietic stem cell transplantation (HCT) can arrest the progression of cerebral disease (Aubourg et al., 1990; Gupta et al., 2022). However, early initiation is essential for favorable clinical outcomes, underscoring the critical importance of early detection. Over 80% of women with ALD develop a slowly progressive spinal cord disease that typically manifests in the fifth decade of life and progresses more slowly than it does in men (Engelen et al., 2014; Huffnagel et al., 2019a). Adrenocortical failure and cerebral demyelination are extremely rare in females. Currently, no disease-modifying treatment is available for spinal cord disease in either males or females.

Because of the narrow treatment window for CALD and the risk of undetected adrenocortical insufficiency, it is essential to identify affected individuals early. Newborn screening (NBS) for ALD provides an opportunity to identify patients before symptoms appear. This allows for close monitoring and prompt intervention before irreversible damage occurs (Engelen et al., 2022). NBS involves measuring C26:0 lysophosphatidylcholine (LPC(26:0)) in dried blood spots (Hubbard et al., 2009), followed by *ABCD1* variant analysis to confirm the results (Boehm et al., 1999). Since New York State introduced NBS for ALD in 2013 (Vogel et al., 2015), it has been implemented in most U.S. states, Taiwan (Chen et al., 2022), and the Netherlands (Albersen et al., 2023). Several other countries, including Italy, Israel, Japan and Spain, are running pilot programs (Bonaventura et al., 2022; Shimozawa et al., 2021).

Central to NBS for ALD is the measurement of LPC(26:0), a biomarker that is consistently elevated in affected individuals (Hubbard et al., 2009). Beyond its established role in newborn screening, LPC (26:0) has attracted increasing attention as a diagnostic and prognostic biomarker, a readout of therapeutic response, and a potential contributor to ALD pathology. This review addresses the biochemical origin, analytical detection, and clinical applications of LPC(26:0) in ALD.

2. The biochemical hallmark of ALD

The first indications of an underlying metabolic cause of ALD came from pathological autopsy and postmortem tissue observations in the early 1970s. Thin-layer chromatography revealed an increase in esterified cholesterol in cerebral white matter (Forsyth et al., 1971), and electron microscopy showed unusual striations in adrenocortical cells consisting of intracytoplasmic lamellae and lamellar lipid inclusions. Similar inclusions were found in testicular cells, Schwann cells, and brain macrophages (Powers and Schaumburg, 1974; Schaumburg et al., 1975). The observation that this striated material was resistant to acetone and ethanol extraction, yet soluble in nonpolar solvents such as hexane and chloroform, pointed to the accumulation of an unusually nonpolar substance (Johnson et al., 1976). Subsequent biochemical analysis revealed that the inclusion bodies contained cholesterol, phospholipids, and gangliosides esterified with saturated very long-chain fatty acids (VLCFAs) (Igarashi et al., 1976). This defined ALD as a lipid storage disease and established aberrant VLCFA metabolism as the central pathogenic factor. The identification of VLCFAs as the primary accumulating species laid the groundwork for developing biochemical diagnostic tools, most notably plasma VLCFA analysis and, later, LPC(26:0) measurement.

3. Biochemical origin and metabolism of LPC(26:0)

LPC is one of the most abundant lysoglycerophospholipids in blood and tissues. It is continuously generated and removed as part of the normal turnover of phosphatidylcholine (PC) (Law et al., 2019). Each LPC molecule carries a single fatty acid of variable chain length and degree of saturation at the sn-1 or sn-2 position of the glycerol backbone and is linked to a phosphocholine headgroup (Fig. 1). In plasma, sn-1 acyl-LPC species are several times more abundant than sn-2 isomers (Law et al., 2019).

Most circulating LPC arises from the enzymatic remodeling of PC (Fig. 2). Secreted and lipoprotein-associated phospholipase A2 (PLA2) hydrolyze PC to LPC and a free fatty acid (Tan et al., 2020), while lecithin:cholesterol acyltransferase (LCAT) generates LPC by transferring a fatty acid from PC to cholesterol within lipoprotein particles (Subbaiah et al., 1992). Endothelial lipase (LIPG), located at the luminal surface of vascular endothelial cells, contributes to circulating LPC by hydrolyzing PC in high-density lipoprotein (HDL) particles (McCoy et al., 2002; Riederer et al., 2011; Tan et al., 2020). Non-enzymatic oxidation and cell damage, particularly under conditions of cellular stress, inflammation, and tissue injury, also increase LPC formation (Law et al., 2019; Liu et al., 2020).

Once formed, LPC is not freely soluble. In plasma, it is predominantly bound to albumin, with smaller fractions associated with HDL and other lipoproteins, as well as erythrocytes and platelets. Intracellularly, LPC is generally short-lived. First, PLA2 converts PC to LPC and a free fatty acid. Then lysophosphatidylcholine acyltransferases (LPCATs/LPLATs) rapidly reacylate LPC back to PC using acyl-CoA substrates. This Lands' cycle maintains tight control over LPC concentrations and shapes the fatty acid composition of cellular membranes (Law et al., 2019; Prabutzki et al., 2024).

From a clinical perspective, the dynamic nature of the LPC–PC cycle means that any alteration in PC remodeling, lipoprotein metabolism, or

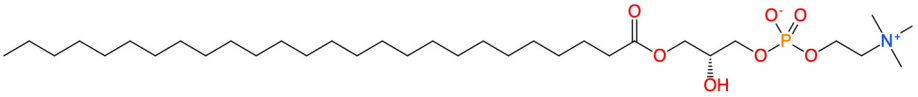

Fig. 1. Chemical structure of C26:0-lysophosphatidylcholine (LPC(26:0)). LPC(26:0) consists of hexacosanoic acid (C26:0) esterified at the sn-1 position of the glycerol backbone, a free hydroxyl group at the sn-2 position, and a phosphocholine headgroup.

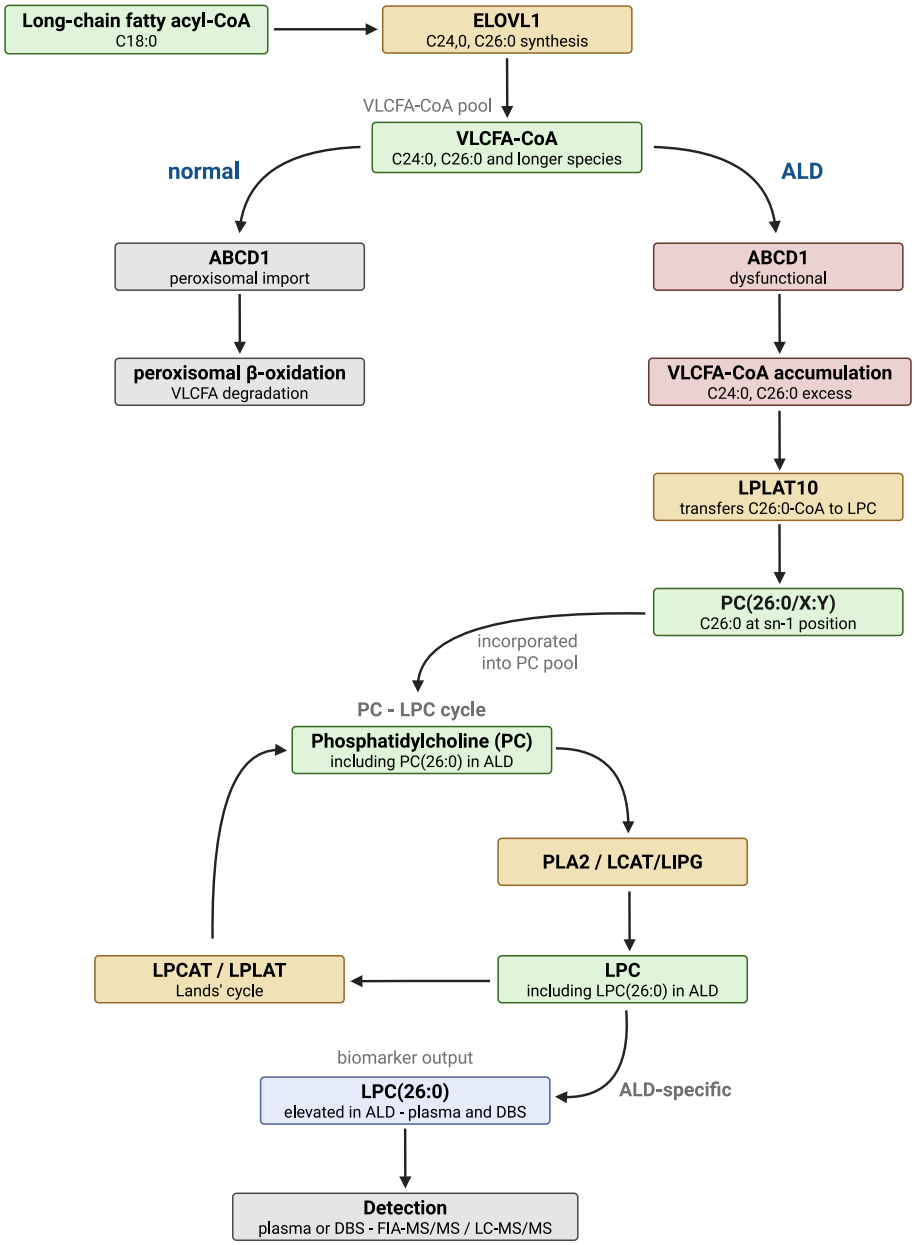

Fig. 2. Biosynthesis and metabolism of LPC(26:0) in ALD. Under normal conditions, ELOVL1 elongates long-chain fatty acyl-CoA to VLCFA-CoA, which is then imported into peroxisomes by ABCD1 for β-oxidation. Phosphatidylcholine (PC) undergoes continuous remodeling through the Lands cycle, generating LPC via phospholipase A2 (PLA2), lecithin:cholesterol acyltransferase (LCAT), and endothelial lipase (LIPG), with reacylation back to PC by lysophosphatidylcholine acyltransferase (LPCAT) and lipoprotein lipase (LPL). In ALD, however, ABCD1 dysfunction leads to VLCFA-CoA accumulation. Lysophospholipid acyltransferase 10 (LPLAT10) then transfers C26:0-CoA to LPC, producing PC(26:0/X:Y), where the 26:0 acyl chain is combined with a variable acyl chain, with X denoting carbon number and Y denoting the number of double bonds. This PC(26:0/X:Y) is subsequently hydrolyzed by PLA2, releasing LPC(26:0) into circulation. Elevated levels of LPC(26:0) are measurable in plasma or dried blood spots using FIA-MS/MS or LC-MS/MS. Created in BioRender. Kemp, S. (2026) https://BioRender.com/515pzkp.

acyl-CoA pools can modify the abundance and acyl-chain profile of LPC species in the blood. In peroxisomal disorders, such as ALD, disruption of VLCFA handling upstream of this cycle is expected to leave a clear biochemical fingerprint in the LPC pool.

In ALD, impaired peroxisomal β-oxidation of VLCFAs leads to the accumulation of VLCFA-CoA species. These VLCFAs are incorporated into various lipids, including phosphatidylcholine, triglycerides and sphingolipids (Jaspers et al., 2024a; Jaspers et al., 2024b), and once present, VLCFA-containing PC species serve as substrates for LPC production pathways. This gives rise to VLCFA-containing LPC species in

tissues and circulation.

LPC(26:0), in which hexacosanoic acid (C26:0) is esterified to the sn-1 or sn-2 position of the glycerol backbone (Hama et al., 2026; Jaspers et al., 2024a), is the best-characterized VLCFA-containing LPC species in ALD and the primary target of screening and diagnostic assays (Hubbard et al., 2006, 2009). As with other LPC species, the sn-1 isomer of LPC(26:0) is several times more abundant than the sn-2 isomer (Hama et al., 2026; Jaspers et al., 2024a; Law et al., 2019).

The enzymatic machinery responsible for generating LPC(26:0) was elucidated through a combination of knockdown experiments, substrate specificity assays and stable isotope tracing that identified lysophospholipid acyltransferase 10 (LPLAT10, also known as LPCAT4/LPEAT2/AGPAT7) as the enzyme that incorporates C26:0-CoA into 2-acyl-LPC. This process produces PC species with a C26:0 moiety at the sn-1 position (Hama et al., 2026). These VLCFA-containing PC species are the direct precursors of LPC(26:0), which is released into the cellular and circulating pool by subsequent hydrolysis by phospholipase A2. Consistent with this, genetic ablation of LPLAT10 in ALD patient-derived fibroblasts significantly reduced LPC(26:0) levels. LPLAT10 exhibits broad acyl-CoA donor selectivity, accepting saturated fatty acids ranging from C16 to C30. However, it displays striking specificity for LPC as the acceptor substrate. C26:0-CoA is efficiently transferred to LPC, but not to lysophosphatidylethanolamine (LPE) (Hama et al., 2026). Structural modelling and molecular dynamics simulations revealed that this selectivity is conferred by a conserved W-X-W motif, in which two tryptophan residues coordinate the trimethylamine headgroup of PC through cation–π interactions. In the absence of LPLAT10, C26:0 is preferentially redirected toward sphingolipid synthesis, resulting in the accumulation of ceramide and sphingomyelin rather than LPC (Hama et al., 2026).

Beyond LPC(26:0), multiple other VLCFA-containing LPC species have been detected in body fluids and tissues of patients with ALD, spanning chain lengths up to 34 carbon atoms in plasma and extending to even longer species in central nervous system (CNS) tissue. These species are predominantly saturated or monounsaturated (Jaspers et al., 2024a; Jaspers et al., 2024b). The relative contribution of individual LPC-generating pathways to circulating LPC(26:0) levels remains undefined. Similarly, the extent to which circulating LPC(26:0) derives from the liver or other cell types has not been systematically determined.

4. LPC(26:0) as a diagnostic marker

Plasma VLCFA analysis became the cornerstone of biochemical diagnosis for peroxisomal beta-oxidation disorders, including ALD, Zellweger spectrum disorders and single enzyme deficiencies. It remained the standard for decades, with analyses traditionally performed using gas chromatography (GC)-based methods (A. B. Moser et al., 1999; H. W. Moser et al., 1991; Vreken et al., 1998). These assays are robust, reproducible, and well-standardized. Despite the emergence of LPC(26:0)-based assays, GC-based VLCFA analysis remains the most widely used diagnostic method in most laboratories worldwide. However, this method requires labor-intensive extraction and derivatization steps, resulting in relatively long turnaround times. Although widely used, plasma VLCFA measurements have recognized limitations. In women with ALD, 15–20% may have VLCFA values within the reference range. This can result in false-negative results and the need for molecular testing or repeat biochemical assessment (A. B. Moser et al., 1999). Conversely, false-positive VLCFA elevations have been described in several acquired or nutritional conditions, including diabetic ketoacidosis, ketogenic diets, and hemolysis (Brown et al., 1982; Kishimoto et al., 1980; Theda et al., 1993). Additionally, false-positive VLCFA elevations have been observed in the context of hyperlipidemia, where total cholesterol correlates positively with VLCFA levels (Rattay et al., 2020; Spreghini et al., 2024). Non-fasted sampling can also complicate interpretation. Consuming VLCFA-rich foods, such as peanuts or peanut butter, shortly before blood collection can acutely increase plasma VLCFA levels into the abnormal range (Lam et al., 2012). This is likely due to the transient enrichment of VLCFA-containing lipoprotein cholesterol esters (Engelen et al., 2010; Wanders et al., 2010).

In response to these limitations, the diagnostic performance of conventional plasma VLCFA analysis was compared with the performance of measuring LPC(26:0) by tandem mass spectrometry in plasma and dried blood spots (DBS) (Huffnagel et al., 2017; Jaspers et al., 2020). In a cohort that included patients with ALD, Zellweger spectrum disorder, and healthy controls, LPC(26:0) achieved complete separation between patients and controls. This was true even for females with ALD, for whom plasma VLCFA analysis yields false-negative results in 15% to 20% of cases. In contrast, total C26:0 and the C26:0/C22:0 ratio produced false-positives and negatives (Huffnagel et al., 2017; Jaspers et al., 2020). A larger, multicenter study of 330 individuals with peroxisomal β-oxidation defects and 407 controls confirmed these findings (Morales-Romero et al., 2024). Importantly, LPC(26:0) analysis by FIA-MS/MS or LC-MS/MS is faster and simpler than GC-based VLCFA assays. Run times are typically a few minutes, and derivatization is not needed (Hubbard et al., 2009; Klouwer et al., 2017). To date, there is no evidence that LPC(26:0) levels are affected by short-term dietary VLCFA intake. These data establish LPC(26:0) as a more sensitive and specific diagnostic test for suspected peroxisomal β-oxidation defects than traditional plasma total VLCFA analysis.

LPC(26:0) quantification is not restricted to plasma. Multiple screening and diagnostic studies demonstrate that LPC(26:0) in DBS is a reliable marker for ALD and Zellweger spectrum disorder (Hubbard et al., 2006, 2009; Huffnagel et al., 2017; Jaspers et al., 2020; Klouwer et al., 2017). In paired samples, LPC(26:0) concentrations in DBS strongly correlate with plasma values (Spearman's rho $\approx$ 0.96), indicating that both matrices reflect the circulating LPC(26:0) pool. This finding demonstrates that both matrices can be used in clinical practice (Jaspers et al., 2020). Analyte stability studies indicate that LPC(26:0) remains stable across a wide range of storage temperatures and for prolonged periods (months to years) when stored with desiccant (Haynes and De Jesus, 2015). This finding supports the use of plasma and DBS LPC(26:0) analysis in centralized testing, retrospective analysis, and long-term biobanking for research purposes.

DBS sampling also offers clear logistical and practical advantages over plasma sampling. Finger-prick collection is minimally invasive and can be performed outside of hospital settings. It also requires less specialized training than conventional venous blood sampling (McDade et al., 2007), making sampling at home or in local care settings feasible. DBS cards can be shipped at ambient temperature via regular mail without the need for dry ice, temperature monitoring, or rapid courier services, in contrast to plasma and whole blood, which usually require controlled conditions and expedited transport. However, DBS does not currently replace plasma in the full diagnostic workup of peroxisomal disorders. Full biochemical characterization extends beyond VLCFA-related markers and includes measuring phytanic acid, pristanic acid, di- and trihydroxycholestanoic acids, and plasmalogens in plasma and erythrocytes (Wanders and Waterham, 2006). Currently, these are not yet routinely validated in DBS. Consequently, plasma remains indispensable for confirmatory testing and subclassification of peroxisomal disorders. However, LPC(26:0) in plasma or DBS is increasingly recognized as the primary screening and diagnostic biomarker for ALD and related peroxisomal β-oxidation defects.

5. Analytical detection and quantification of LPC(26:0)

The concentration of LPC(26:0) in plasma and DBS is measured by tandem mass spectrometry (MS/MS) using the m/z 636.5 → 184.1 (or 104.1) precursor-to-product ion transition with a tetradeuterated internal standard D_4-LPC(26:0) for quantification. Two analytical platforms are used: flow injection analysis tandem mass spectrometry (FIA-MS/MS) and liquid chromatography tandem mass spectrometry (LC-

MS/MS). FIA-MS/MS offers high throughput, typically taking one and a half to two minutes per sample, and can be integrated with routine newborn screening workflows for amino acids and acylcarnitines using a single DBS extraction (Haynes and De Jesus, 2016; Turgeon et al., 2015). However, FIA-MS/MS does not chromatographically separate LPC(26:0) from isobaric lipid species with the same nominal mass. These interferents, which have not been fully characterized, can cause the LPC (26:0) signal to appear elevated, resulting in false-positive screening results (Turgeon et al., 2015). LC-MS/MS resolves this limitation by separating compounds chromatographically prior to mass spectrometric detection, thereby achieving superior analytical specificity. For this reason, a two-tier approach has been adopted in many NBS programs. FIA-MS/MS serves as the primary, high-throughput screen, and LC-MS/MS is used as a confirmatory, second-tier assay for samples with elevated LPC(26:0) (Hubbard et al., 2009; Turgeon et al., 2015). This approach reduces false-positive rates while maintaining the throughput necessary for population-scale screening.

An important preanalytical consideration is the effect of neonatal hematocrit on DBS LPC(26:0) values. Since LPC(26:0) is enriched in red blood cells and red blood cell counts are higher in neonates than in older individuals, DBS LPC(26:0) concentrations are significantly higher in neonates than in older subjects (Lund et al., 2026b). Plasma LPC(26:0), however, is not subject to this effect (Lund et al., 2026b). This has direct implications for interpreting DBS results during the neonatal period, which are discussed further in the newborn screening section.

6. LPC(26:0) in newborn screening

In February 2016, ALD was added to the Recommended Uniform Screening Panel (RUSP) in the United States (Kemper et al., 2017), following its implementation in the New York State newborn screening program in December 2013 (A. B. Moser et al., 2016; Vogel et al., 2015). Newborn screening for ALD has been implemented in nearly all U.S. states, as well as in Taiwan (Chen et al., 2022) and the Netherlands (Albersen et al., 2023; Barendsen et al., 2020). Pilot programs are ongoing in Japan (Shimozawa et al., 2021), Israel, Italy (Bonaventura et al., 2022), and Spain. NBS is based on measuring LPC(26:0) in DBS using LC-MS/MS. This method was first validated by Hubbard et al. following the demonstration that LPC(26:0) levels are elevated in the plasma and DBS of ALD patients (Hubbard et al., 2006, 2009). The prospective application of this method to nearly 4,700 newborn blood spot samples confirmed its feasibility for population-level screening with no observed false-positive results (Theda et al., 2014). In parallel, C26:0-carnitine was identified as a potential alternative screening marker. It was identified in the brain and spinal cord tissue of *Abcd1* knockout mice with oligodendrocyte-specific ELOVL1 overexpression, and elevated levels were confirmed in DBS from ALD patients (M.-C. C. van de Beek et al., 2016). C26:0-carnitine may be a more practical screening marker than LPC(26:0) because it can be measured using routine acylcarnitine analysis, eliminating the need for a dedicated method (Haynes and De Jesus, 2016; Sandlers et al., 2012). However, a comparison of the sensitivities of C26:0-carnitine and LPC(26:0) in DBS from approximately 270,000 newborns in the New York State screening program revealed that C26:0-carnitine had a sensitivity of only 83%, compared to 100% for LPC(26:0). These data confirmed that LPC(26:0) is a superior first-tier marker for ALD newborn screening (Huffnagel et al., 2017).

NBS for ALD primarily aims to identify male newborns, who are at risk of developing adrenal insufficiency and/or cerebral ALD in childhood (Engelen and Kemp, 2025). Whether to screen female newborns is an ongoing point of debate with clinical and ethical dimensions (Barendsen et al., 2020; Currier, 2022; Yska et al., 2023). According to the Wilson and Jungner criteria, universal screening for females is difficult to justify, as they generally do not experience life-threatening complications during childhood, and there is no disease-modifying treatment for myelopathy. Furthermore, early detection could impose a psychological burden on families when they are informed of an untreatable, late-onset condition in an otherwise healthy child (Currier, 2022; Lund et al., 2026b; Yska et al., 2023). Nevertheless, early diagnosis in girls may offer indirect benefits, including reduced diagnostic delay, informed family planning, and extended family screening. A survey of ALD patients reflected this tension: 80% favored screening both boys and girls, motivated by early awareness, monitoring opportunities, and family planning. However, 20% preferred screening only boys, citing the absence of childhood symptoms and the lack of available treatment for females as the main reasons (Yska et al., 2023).

Following the Wilson and Jungner criteria, the Netherlands and Japan implemented boys-only NBS programs (Barendsen et al., 2020; Shimozawa et al., 2021). The Dutch program uses an algorithm that includes X-chromosome counting to prevent errors in sex determination on the heel-prick card (Albersen et al., 2023; Barendsen et al., 2020).

Regardless of which sex is screened, a fundamental challenge in any NBS program is to minimize false-positive results while maintaining sensitivity. An NBS result that is positive on the screen is not a confirmed diagnosis and requires further biochemical and molecular confirmation. In ALD NBS, the LPC(26:0) cutoff was set to minimize false negatives, prioritizing sensitivity over specificity. Consequently, many newborns with borderline LPC(26:0) elevations and *ABCD1* variants that have never been reported in patients with confirmed clinical disease are identified. These variants are classified as variants of uncertain significance (VUS), and the likelihood of identifying a VUS in *ABCD1* is three times higher in NBS than in clinical testing (Kemp et al., 2023; Lund et al., 2026b). The *ABCD1* Variant Database (https://adrenoleukodystrophy.info) supports the interpretation of these variants by cataloging over 1300 pathogenic and benign variants and providing essential context for variant classification (Kemp et al., 2001; Mallack et al., 2022). The clinical relevance of early detection for newborns with borderline LPC(26:0) elevation combined with a VUS remains unclear. Furthermore, the magnitude of LPC(26:0) elevation provides additional diagnostic information. Values clearly within the ALD diagnostic range are more likely to reflect a true peroxisomal β-oxidation defect. However, borderline elevations require careful clinical and biochemical follow-up before a confirmed diagnosis can be made, particularly when combined with a VUS in *ABCD1* (Lund et al., 2026b).

An important practical consideration for confirmatory testing is how neonatal hematocrit affects DBS LPC(26:0) values (Lund et al., 2026b). Since newborns have an elevated red blood cell count which decreases gradually during the first months of life, DBS LPC(26:0) concentrations during the neonatal period are significantly higher than in older individuals (Lund et al., 2026b). However, plasma LPC(26:0) levels are not affected by this age-dependent difference. DBS LPC(26:0) concentrations stabilize once red blood cell counts normalize after approximately 100 days (Jaspers et al., 2024b; Lund et al., 2026b). This has direct implications for confirmatory testing. Diagnostic cutoffs derived from older individuals and confirmed ALD patients cannot be applied directly to DBS samples collected in the neonatal period. Therefore, confirmatory DBS sampling should be performed after 100 days of age to ensure accurate interpretation.

7. Specificity and differential diagnosis of elevated LPC(26:0)

LPC(26:0) is not specific to ALD but serves as a sensitive biomarker indicating impaired peroxisomal VLCFA β-oxidation. Elevated LPC (26:0) levels are found across a range of disorders, including Zellweger spectrum disorders, acyl-CoA oxidase 1 (ACOX1) deficiency, D-bifunctional protein (HSD17B4) deficiency, contiguous ABCD1/DXS1357E deletion syndrome (CADDS), and ACBD5 deficiency. Patients with Zellweger spectrum disorders tend to have higher plasma LPC(26:0) concentrations than patients with ALD, reflecting the more generalized peroxisomal dysfunction in biogenesis disorders (Jaspers et al., 2020; Morales-Romero et al., 2024). Because elevation of LPC(26:0) is not disease-specific, a positive result in newborn screening or diagnostic

testing requires confirmatory molecular analysis to establish the underlying diagnosis. This includes *ABCD1* sequencing for suspected ALD and *PEX* gene panel testing for suspected Zellweger spectrum disorder. The differential diagnosis of elevated LPC(26:0) extends to other conditions that cause transient secondary peroxisomal dysfunction. Elevated levels have been reported in neonatal lupus erythematosus, where LPC(26:0) normalized after birth in three cases (Niehaus et al., 2023). This finding is consistent with the hypothesis that the elevation reflects a transient inflammatory response to maternal autoantibodies rather than a primary peroxisomal defect. Elevated LPC(26:0) has also been reported in Aicardi-Goutières syndrome, an interferonopathy in which the mechanism underlying LPC(26:0) accumulation remains unclear (Armangue et al., 2017; Tise et al., 2021). Together, these findings establish LPC(26:0) as a sensitive first-tier biomarker for peroxisomal β-oxidation dysfunction, with disease-specific molecular confirmation being an essential second step in the diagnostic process.

8. LPC(26:0) as a prognostic marker

A lipidomics study in a large, clinically well-phenotyped ALD cohort showed VLCFA enrichment across multiple lipid classes, including LPC, PC, TG, and sphingomyelins. Higher levels were associated with leukodystrophy, adrenal insufficiency, and severe spinal cord disease in men, and with disease severity and X-inactivation patterns in women (Jaspers et al., 2024b). These findings contrast with those of older, smaller studies that failed to identify clear correlations with disease severity, likely due to their cross-sectional design, limited phenotyping, and lack of long-term follow-up (Boles et al., 1991; A. B. Moser et al., 1999; H. W. Moser et al., 1984). In ALD, symptom-based stratification is difficult because the disease is progressive. The absence of symptoms at the time of assessment and plasma sampling does not rule out their development later in life.

These findings indicate that ALD disease severity is reflected by a VLCFA-containing lipid signature. The strongest relationships are observed with longer, more saturated species (Jaspers et al., 2024b). Within this framework, LPC(26:0) is best regarded as a prominent component rather than the sole biologically relevant marker. From a clinical standpoint, LPC(26:0) is currently the most practical indicator of this signature. Targeted FIA-MS/MS or LC-MS/MS assays for LPC(26:0) in plasma or dried blood spots have been widely implemented in diagnostic laboratories and newborn screening programs. These assays provide robust quantitative measurements suitable for routine diagnostics, longitudinal monitoring, and interlaboratory comparison. This offers a clear advantage in clinical translatability over other VLCFA lipids, which currently require advanced lipidomics platforms and remain semi-quantitative (Jaspers et al., 2024a). Targeted plasma LPC(26:0) closely mirrors these lipidomics results and supports its role as a biomarker of disease burden (Jaspers et al., 2020; Jaspers et al., 2024b). However, several VLCFA-containing lipid species identified in these studies are more strongly associated with disease severity in ALD than LPC(26:0) is, suggesting that broader lipidomic profiling may further improve prognostic accuracy beyond LPC(26:0) alone.

Longitudinal data from a small group of males who had samples collected before and after the onset of cerebral disease showed that VLCFA-containing lipids were markedly elevated before overt cerebral ALD and remained high thereafter. This suggests that elevated LPC(26:0) reflects underlying susceptibility rather than active leukodystrophy. However, sample numbers in this subset were limited, and larger prospective studies are needed to establish predictive cutoffs and inform clinical decision thresholds for individual patients. Data from newborn screening cohorts are also consistent with a prognostic signal. Reports from Minnesota and Italy show that higher LPC(26:0) levels at birth correlate with the likelihood of developing disease manifestations in early childhood, with higher values observed in boys who subsequently developed clinical phenotypes (Billington et al., 2025; Bonaventura et al., 2025). These findings suggest that NBS cutoffs could be refined to more accurately identify individuals who would benefit from an early diagnosis and subsequent follow-up care while reducing the surveillance burden on families (Billington et al., 2025; Engelen and Kemp, 2025; Lund et al., 2026b; Rayannavar et al., 2025). Furthermore, these findings have prompted proposals for risk-stratified surveillance protocols. Results from the Grey Zone Project suggest that LPC(26:0) levels could enable risk stratification, allowing VUSs to be reclassified as either "lower risk AI/CALD" or "at risk AI/CALD" (Lund et al., 2026b). However, this approach requires further validation before implementation to ensure the benefits outweigh the potential risks.

Taken together, the current literature suggests that the prognostic signal in ALD is embedded within a broad spectrum of VLCFA-containing lipids. Currently, LPC(26:0) is the leading biomarker because it is the most analytically mature readout of that broader lipid abnormality. It is the best available targeted proxy for a wider VLCFA-lipid disease-severity phenotype, and it has clear potential for future risk stratification and monitoring as prospective validation matures.

9. Potential role of LPC(26:0) in ALD pathology

LPC can exert both pro- and anti-inflammatory effects. Its immunomodulatory properties are strongly influenced by its molecular structure, including the length of the acyl chain and the degree of unsaturation (Prabutzki et al., 2024). The biological activities of LPC species are partly mediated through receptor-dependent signaling pathways. Shorter-chain LPC species, such as LPC(16:0) and LPC(18:1), activate pattern recognition receptors, including Toll-like receptors 2 and 4 (TLR2/TLR4). This activates NF-κB and leads to pro-inflammatory or immunomodulatory signaling in monocytes, macrophages, and endothelial cells downstream (Carneiro et al., 2013). It is unknown whether very-long-chain LPC species, such as LPC(26:0), engage these or other receptor pathways. In addition to receptor-mediated effects, LPC can directly alter membrane structure and mechanics. Biophysical studies demonstrate that LPC insertion alters bilayer curvature, modulates ion channel function, and facilitates membrane permeabilization (Lundbaek and Andersen, 1994). Molecular dynamics simulations suggest that very-long-chain LPC species (C24:0 and C26:0) deeply embed in sphingomyelin bilayers. These species cooperatively reshape lipid packing, reduce lipid mobility, and decouple membrane leaflets (Cabrera et al., 2026). Due to its exceptional acyl chain length and resulting ability to interdigitate with ordered membranes, LPC(26:0) may exert many of its biological effects through membrane-disrupting or membrane-mechanical mechanisms rather than through classical receptor-mediated signaling. However, this has not been systematically investigated. LPC species play an important physiological role in delivering omega-3 fatty acids, particularly docosahexaenoic acid (DHA), to the CNS via the major facilitator superfamily domain-containing protein 2 A (MFSD2 A) at the blood-brain barrier (Nguyen et al., 2014). Whether LPC(26:0) interacts with this transporter has not been experimentally investigated.

Saturated LPC species, such as LPC(16:0), are commonly used in vitro and in vivo to induce demyelination by disrupting lipid membranes (Plemel et al., 2018). In this case, LPC primarily acts as a lipid-disrupting agent, destabilizing myelin membranes rather than acting via a single receptor pathway (Birgbauer et al., 2004). It should be noted that these experimental models of LPC-induced demyelination and neuroinflammation have two significant limitations. First, they typically use supraphysiological concentrations of LPC that do not reflect endogenous levels, even under pathological conditions. Second, the LPC species used — predominantly C14:0 to C18:1 — do not accumulate in ALD. Endogenous VLCFA-containing LPC species, such as LPC(24:0) and LPC (26:0), are present at far lower concentrations in plasma and tissue. Specific toxicity data for these species at physiologically relevant concentrations is currently lacking. However, one notable exception is that intracortical injection of LPC(24:0) induces microglial activation and neuronal apoptosis, whereas LPC(16:0) does not in the same model

(Eichler et al., 2008). This finding suggests that chain length is a critical determinant of neurotoxic potential, supporting the hypothesis that LPC (26:0) may contribute to ALD pathology beyond its role as a biomarker. Further support for the direct effect of VLCFAs on myelin structure comes from quantitative magnetic resonance imaging (qMRI) studies in ALD patients. In a cohort of 81 adults with ALD, the myelin-to-water ratio and the neurite density index were significantly lower in the normal-appearing white matter of males with and without cerebral ALD compared to controls. This suggests that microstructural abnormalities may precede overt lesion formation (Yska et al., 2025). Interestingly, the myelin-water T2 relaxation time was shorter in ALD patients than in controls, which is contrary to what would be expected from classical demyelination. This may indicate that increased VLCFA incorporation into myelin lipids alters its structural compactness. If confirmed in future studies, this may provide a mechanistic link between VLCFA-containing lipid accumulation and early white matter pathology in ALD independent of overt demyelination (Yska et al., 2025).

The pro-inflammatory effects of LPC include the upregulation of endothelial adhesion molecules (e.g. ICAM-1), increased mitochondrial reactive oxygen species production, and enhanced monocyte recruitment across the endothelium (Knuplez and Marsche, 2020). LPC also promotes monocyte chemotaxis and induces the secretion of chemokines and cytokines (e.g. MIP-2, IL-6, IL-8, IL-1β) from macrophages and monocyte-derived cells, often at nanomolar to micromolar concentrations (Dzobo et al., 2024). These activities are most consistently attributed to saturated and some monounsaturated LPC species. However, polyunsaturated LPCs (e.g. LPC(20:4), LPC(22:6)) can counteract LPC (16:0)-induced inflammation in vivo (Kettwig et al., 2021), illustrating the species-dependent pro- versus anti-inflammatory actions of LPCs (Knuplez and Marsche, 2020; Prabutzki et al., 2024).

These observations are particularly relevant in the context of ALD, where VLCFA-containing LPC species accumulate systemically and in CNS lipoproteins (Bougnères and Le Stunff, 2025; Fujitani et al., 2024; Gong et al., 2017). In human hiPSC-derived astrocytes, ABCD1 deficiency results in reduced peroxisomal VLCFA β-oxidation and substantially elevated LPC(26:0) levels, underscoring the significance of LPC (26:0) accumulation in CNS-relevant glial cells (Ferrer et al., 2025). In ABCD1-deficient microglia, LPC(26:0) exacerbates neurotoxicity by upregulating the opsonin MFGE8. This increases phagocytic activity and promotes neuronal injury. Blocking MFGE8 attenuates LPC(26:0)-driven phagocytic neurodegeneration (Gong et al., 2017). Together, these findings highlight the pathogenic potential of saturated VLCFA-containing LPC species in vulnerable white matter regions, including the corpus callosum and spinal cord.

10. LPC(26:0) as a pharmacodynamic biomarker

The analytical maturity of LPC(26:0) measurement has established its use as a practical readout in early drug discovery studies and as a pharmacodynamic biomarker across therapeutic strategies in ALD. Due to its relevance to the disease, sensitivity, and ease of quantification by LC-MS/MS, LPC(26:0) has been used in preclinical and clinical studies to evaluate compounds and interventions that reduce VLCFA burden.

Nutritional intervention with nervonic acid (C24:1n-9), a monounsaturated VLCFA found in myelin, has been explored as a strategy to reduce VLCFA burden. This approach is based on the experimental observation that monounsaturated VLCFAs compete with saturated VLCFAs for incorporation into complex lipids (Rizzo et al., 1989). In a four-week dietary intervention study in *Abcd1* knockout mice, nervonic acid supplementation reduced plasma LPC(26:0) by approximately 60% within one week and brain LPC(26:0) by approximately 56% after four weeks (Li et al., 2026). However, these preclinical findings require validation in human studies before conclusions about therapeutic efficacy can be drawn.

Pharmacological inhibition of ELOVL1, the key enzyme in VLCFA synthesis (Ofman et al., 2010; Ohno et al., 2010), reduces C26:0 levels in patient-derived cells, as well as in the brain and spinal cord of *Abcd1* knockout mice (Come et al., 2021; Huang et al., 2025). Blood LPC(26:0) has been used as the primary pharmacodynamic readout in these preclinical studies. It responds rapidly and dose-dependently to ELOVL1 inhibition, normalizing to near wild-type levels in blood within one week of dosing in *Abcd1* knockout mice (Boyd et al., 2021). Since LPC (26:0) reflects changes in the upstream VLCFA-CoA pool via LPLAT10-mediated incorporation into phosphatidylcholine (Fig. 2), it can capture changes in VLCFA synthesis well. Despite these promising preclinical results, the therapeutic index of ELOVL1 inhibitors remains a critical challenge, as dose-limiting toxicities have been observed across multiple compound series and species (Boyd et al., 2021; Come et al., 2021; Huang et al., 2025).

Modulating LPLAT10 activity itself represents a more distal intervention point. Reducing LPLAT10-mediated incorporation of C26:0-CoA into the LPC pool could theoretically lower circulating LPC(26:0) independently of VLCFA synthesis. However, without LPLAT10 activity, C26:0-CoA is preferentially redirected toward sphingolipid synthesis. This results in the accumulation of ceramide and sphingomyelin rather than LPC (Hama et al., 2026). The consequences of this redistribution for ALD pathology are unknown and would require careful evaluation before LPLAT10 modulation could be considered a viable therapeutic strategy.

A conceptually distinct strategy is to redirect VLCFA metabolism by increasing fatty acid desaturation before elongation. This approach is supported by evidence showing that the saturation status of VLCFAs is a critical determinant of their toxicity. Exposure to saturated VLCFAs (C26:0) induces endoplasmic reticulum (ER) stress, oxidative stress, and mitochondrial dysfunction in cells derived from patients with ALD (Fourcade et al., 2008; Lopez-Erauskin et al., 2013; M. C. van de Beek et al., 2017; Vargas et al., 2004). Conversely, monounsaturated VLCFAs (C26:1) do not induce an ER stress response (M. C. van de Beek et al., 2017) and may attenuate ER stress induced by saturated fatty acids (Volmer et al., 2013). Stearoyl-CoA desaturase-1 (SCD1) desaturates long-chain saturated fatty acyl-CoAs, primarily C16:0-CoA and C18:0-CoA, producing monounsaturated C16:1 and C18:1 species that can be elongated into monounsaturated VLCFAs. In ALD models, SCD1 induction reduced C26:0 and LPC(26:0) levels by rerouting fatty acid metabolism away from saturated VLCFA accumulation (Raas et al., 2021). Conversely, SCD1 inhibition increased C26:0 synthesis and blocked the formation of monounsaturated C26:1 species (Raas et al., 2021). For LPC(26:0), this distinction is important because a decrease in saturated LPC(26:0) could indicate that the body is rerouting substrates toward the production of monounsaturated VLCFA-containing lipids rather than normalizing VLCFA metabolism completely. Therefore, SCD1-based strategies would require pharmacodynamic monitoring that goes beyond LPC(26:0) and includes LPC(26:1) and other saturated and monounsaturated VLCFA-containing lipid species. However, because SCD1 is a central regulator of lipogenesis, chronic pharmacological activation would require careful evaluation of systemic metabolic risks.

Gene therapy and hematopoietic stem cell transplantation (HCT) can restore ABCD1 function and arrest the progression of cerebral disease (Aubourg et al., 1990; Cartier et al., 2009; Eichler et al., 2017; Raymond et al., 2019). However, their effects on LPC(26:0) differ markedly. Following HCT, plasma LPC(26:0) concentrations substantially decreased — from a mean of 435 nmol/L before the transplant to 190 nmol/L after 24 months — yet they remain elevated above the reference range (<100 nmol/L). This indicates a partial rather than complete correction of the underlying VLCFA metabolic defect (Jaspers et al., 2024b). In contrast, gene therapy results in only a modest and non-significant decline in plasma LPC(26:0) at 12 months post-treatment (Lund et al., 2026a). These assessments were made at different time points: 24 months after HCT versus 12 months after gene therapy, which may partly explain the difference in magnitude. Nevertheless, the difference likely reflects the substantially lower proportion of gene-

corrected cells achieved with current lentiviral gene therapy protocols, which is typically 10–20% one year after treatment. This is compared with the complete donor chimerism achieved after allogeneic HCT. This results in incomplete restoration of ABCD1 function and correspondingly limited biochemical correction (Lund et al., 2026a).

Taken together, these data support LPC(26:0) as a pharmacodynamic biomarker capable of distinguishing the degree of biochemical correction achieved by different therapeutic approaches. They also underscore its potential utility as an endpoint in future therapeutic trials.

11. Open questions and future directions

Despite significant progress, several fundamental questions about LPC(26:0) remain unanswered and require further investigation. The cellular and tissue origin of circulating LPC(26:0) has not been determined systematically. Although LPLAT10 has been identified as the key enzyme that incorporates C26:0-CoA into the PC pool, the contributions of the liver, adrenal glands, CNS, and other cell types to the circulating LPC(26:0) pool are still unclear (Hama et al., 2026). Clarifying this is important for understanding which compartments drive the biochemical signal measured in plasma and DBS. The precise pathogenic role of LPC (26:0), whether it is primarily a biomarker of VLCFA accumulation or an active mediator of neuroinflammation and demyelination, remains to be established. Experimental evidence points to a direct pathogenic role for LPC(26:0) by the demonstration that LPC(24:0) injection in mouse brain induces microglial activation and neuronal apoptosis, and LPC(26:0) upregulates MFGE8-driven phagocytosis in ABCD1-deficient microglia (Eichler et al., 2008; Gong et al., 2017). However, it has not been demonstrated in humans whether plasma LPC(26:0) levels reflect those in CNS tissue or whether reducing plasma LPC(26:0) translates to reduced CNS toxicity. Whether LPC(26:0) exerts its biological effects primarily through receptor-mediated pathways, membrane-mechanical mechanisms, or both remains an important open question that has not been systematically investigated. The relationship between LPC(26:0) and clinical outcomes requires further prospective validation. Early data from Minnesota and Italy suggest that higher neonatal LPC(26:0) levels predict early-onset disease; however, the cohorts are small, and follow-up is limited (Billington et al., 2025; Bonaventura et al., 2025). Larger prospective studies with standardized clinical endpoints are needed to establish predictive cutoffs and define actionable thresholds for risk stratification in both symptomatic and presymptomatic patients. Standardization of LPC(26:0) assays across laboratories and harmonization of reference materials would strengthen interlaboratory comparability and support multicenter research. Finally, the potential of LPC(26:0) as a pharmacodynamic biomarker in therapeutic trials, including those involving ELOVL1 inhibition, gene therapy, and other emerging interventions, remains largely unexplored. As new treatments enter clinical development, validated biomarkers that reflect target engagement and disease modification will be essential. For strategies that redirect VLCFA metabolism toward monounsaturated species, such as the induction of SCD1, it is essential to concurrently monitor LPC(26:1) and LPC(26:0) to distinguish substrate rerouting from true metabolic normalization.

12. Conclusion

LPC(26:0) has emerged as the central biochemical biomarker of ALD, transforming both diagnosis and newborn screening. Its analytical advantages over conventional plasma VLCFA analysis, including superior sensitivity and specificity, matrix flexibility, speed, and stability, have enabled its widespread implementation in clinical and screening laboratories worldwide. Elucidating the biosynthetic pathway through which LPLAT10 incorporates C26:0-CoA into the LPC pool clarified the biochemical origin of this marker and opened new avenues for understanding VLCFA trafficking in ALD. Beyond its diagnostic role, accumulating evidence positions LPC(26:0) as a disease burden biomarker. Its levels correlate with cerebral ALD, adrenal insufficiency, and spinal cord disease severity. Neonatal LPC(26:0) concentrations correlate with early-onset disease manifestations, supporting risk-stratified surveillance protocols and potentially therapeutic decision thresholds in the future. Concurrently, experimental data implicate VLCFA-containing LPC species, including LPC(26:0), as potential mediators of the neuroinflammatory cascade that drives cerebral disease. This raises the possibility that this biomarker not only reflects disease activity but also contributes to it. Furthermore, LPC(26:0) has been shown to be useful as a pharmacodynamic biomarker, capable of distinguishing the degree of biochemical correction achieved by different therapeutic approaches, ranging from HCT to new strategies, such as ELOVL1 inhibition. Key questions remain. The tissue origin of circulating LPC(26:0), its precise pathogenic contribution in the CNS, and its value as a pharmacodynamic endpoint in therapeutic trials have yet to be fully established. Addressing these issues through prospective cohort studies, standardized assay platforms, and mechanistic research is essential to realizing the full potential of LPC(26:0) — not only as a marker of VLCFA accumulation but also as a tool for precise monitoring and ultimately for guiding personalized treatment decisions in ALD.

CRediT authorship contribution statement

Yorrick R.J. Jaspers: Visualization, Conceptualization, Writing – review & editing, Writing – original draft. **Stephan Kemp:** Visualization, Conceptualization, Writing – review & editing, Writing – original draft. **Marc Engelen:** Writing – review & editing, Writing – original draft. **Inge M.E. Dijkstra:** Writing – original draft.

Funding

Metakids - JelteNextGen Award 2025–116 (to Y.J.).

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Yorrick Jaspers reports financial support was provided by Metakids Foundation. Yorrick Jaspers reports a relationship with Metakids Foundation that includes: funding grants. None has patent NA pending to NA. nothing to declare If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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