



# Leukodystrophies in Children: Diagnosis, Care, and Treatment

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Leukodystrophies are a group of genetically determined disorders that affect development or maintenance of central nervous system myelin. Leukodystrophies have an incidence of at least 1 in 4700 live births and significant morbidity and elevated risk of early death. This report includes a discussion of the types of leukodystrophies; their prevalence, clinical presentation, symptoms, and diagnosis; and current and future treatments. Leukodystrophies can present at any age from infancy to adulthood, with variability in disease progression and clinical presentation, ranging from developmental delay to seizures to spasticity. Diagnosis is based on a combination of history, examination, and radiologic and laboratory findings, including genetic testing. Although there are few cures, there are significant opportunities for care and improvements in patient well-being. Rapid advances in imaging and diagnosis, the emergence of and requirement for timely treatments, and the addition of leukodystrophy screening to newborn screening, make an understanding of the leukodystrophies necessary for pediatricians and other care providers for children.

## INTRODUCTION

Inherited leukodystrophies are a group of genetically diverse diseases with more than 30% mortality by 8 years of age. Leukodystrophies, which are attributable to abnormalities of the brain myelin (white matter), are individually rare but collectively common, with a published incidence of 1 in 4700 live births.<sup>1-4</sup> Leukodystrophies can present at any age from preterm infants and neonates to late adulthood<sup>5,6</sup> and have been reported across all ethnicities and regions of the world.<sup>7-13</sup> Clinical recognition of leukodystrophies accelerated with the widespread clinical adoption of MRI in the 1980s and 1990s,<sup>14,15</sup> and recent improvements in genetic diagnosis techniques have led to specific diagnosis in more than half of all patients with leukodystrophy.<sup>2,16,17</sup>

## abstract

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Today, definitive cures exist only for a few leukodystrophies. However, there is tremendous excitement for patients, providers, and families because of a multitude of clinical trials and genetic therapies that are being pursued and rapidly becoming available.<sup>18</sup> In addition, a crucial point is that all leukodystrophies are treatable. Improved general care and quality of life for patients and their families is recognized as a central goal of treatment. An analogous dramatic example is that of cystic fibrosis, for which average life expectancy has increased from 30 days to 30 years even in the absence of a genetic cure.<sup>18,19</sup> These gains in longevity were largely derived from incremental improvements in the approach to routine care (eg, aggressive physiotherapy, antibiotics), and applying standard preventive health maintenance has the potential to improve overall health.<sup>20</sup>

Because of the potential for treatment when recognized early, the US Health and Human Services Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) Recommended Uniform Screening Panel (RUSP) now recommends universal newborn screening (NBS) for X-linked adrenoleukodystrophy (X-ALD).<sup>21</sup> New York, Connecticut, Pennsylvania, Minnesota, and California now include some leukodystrophies in their NBS panels, and more than 15 states added testing for X-ALD in their panels in 2019 and 2020.<sup>22</sup> Additional states are in the evaluation process for consideration to add X-ALD and/or Krabbe disease to their NBS panels.

The general pediatrician plays an important role for children with leukodystrophies. The pediatrician may need to assist with prompt and appropriate referral for NBS results, provide a medical home for patients

and families as they navigate between different subspecialists for treatments, provide long-term follow-up after therapies such as hematopoietic stem cell transplant (HSCT), and counsel families who have an affected child or an affected relative. These roles for the pediatrician are new and transforming rapidly and often have not been addressed in residency training.

This clinical report from the AAP on leukodystrophies will help guide policy management for NBS, approaches to diagnosis, timing and choice of treatment, and supportive therapies. Leukodystrophies, formerly considered a rare neurologic disorder that would not be seen by a general pediatrician, are relatively common as a group of disorders. Therefore, familiarity with the general principles for diagnosis and supportive management in leukodystrophies is important for all pediatricians. The primary take-home message is that recognizing and diagnosing a leukodystrophy is important, because some leukodystrophies require urgent treatment.

### CATEGORIES AND DISEASES

What is a leukodystrophy? Broadly speaking, it is any genetic disease affecting the myelin of the central nervous system (CNS). Table 1 presents a list of commonly used terms, definitions, and abbreviations used in leukodystrophies. Leukodystrophies fall into broad categories: (1) hypomyelination, in which there is absent or diminished myelin production; (2) dysmyelination, in which there is abnormal myelin development; or (3) demyelination, in which there is loss and/or destruction of previously established myelin. Demyelinating leukodystrophies tend to be the more well-known leukodystrophies, including Krabbe

disease, X-ALD, and metachromatic leukodystrophy (MLD). Better-known hypomyelinating leukodystrophies include Pelizaeus-Merzbacher disease (PMD), RNA polymerase III-related leukodystrophies/4-H syndrome (hypomyelination, hypogonadotropic hypogonadism, and hypodontia), and hypomyelination with atrophy of the basal ganglia and cerebellum. A single disease can fall into more than one category, even in the same individual. Also, this categorization theme is based mostly on the appearance of the leukodystrophy by using MRI, which can be subjective.

There is disagreement over the exact definition of a leukodystrophy and whether certain conditions meet required criteria.<sup>2,3</sup> Further complicating this lack of consensus are differences in the severity of the disease. For example, the exact same genetic mutation of *ABCD1* (the gene responsible for X-ALD) in twin brothers can lead to rapid cerebral demyelination in childhood or to a slow and chronic effect mostly of the peripheral nerves. Finally, next-generation sequencing techniques are revealing complex genotype-phenotype disease relationships of leukodystrophy genes, which were unsuspected and unknown 5 years ago.

One standard for definition of leukodystrophies was published in 2015 based on the consensus opinion of a panel of inherited white matter disease experts.<sup>23</sup> The group classified 30 diseases as leukodystrophies, defined as heritable disorders affecting the white matter of the CNS with or without peripheral nervous system involvement.<sup>23</sup> This does not include acquired CNS myelin disorders, such as multiple sclerosis, and related acquired CNS demyelinating processes. Inborn errors of metabolism, in which the clinical

**TABLE 1** Definitions and Terms Used in the Text

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Brainstem auditory evoked potential: A test for intactness of the auditory nerve and CNS auditory centers.

BMT: often used interchangeably with HSCT or UCB transplant. Used as a treatment of certain leukodystrophies.

CNS: including the brain, spinal cord, retina, and optic and olfactory nerves.

Demyelination: loss and/or destruction of previously established myelin.

Dysmyelination: abnormal myelin development.

EMG: typically performed with NCS, to evaluate muscle and nerve function.

HSCT: transplant of cells derived from a healthy donor source of hematopoietic lineages is curative for a few leukodystrophies (see Table 2). Types, technical aspects, benefits, and risks of transplant vary. The transplant source can be peripheral blood, BMT, or UCB transplant.

Hypomyelination: absent or diminished myelin production.

Leukodystrophy: a heritable disorder affecting the white matter of the CNS with or without peripheral nervous system involvement.<sup>22</sup> This does not include acquired CNS myelin disorders, such as multiple sclerosis and related acquired CNS demyelinating processes.

Leukoencephalopathy (genetic): a disease that may reveal significant white matter changes in the brain but the predominant symptoms of the disease are considered to arise from the gray matter or other organ systems.

MRI: important imaging tool for diagnosis and evaluation of leukodystrophy. Aspects of MRI analysis that may be helpful for diagnosis include T1, T2, and diffusion weighted imaging. For a few leukodystrophies, the specific findings on MRI can help make a diagnosis.

Myelin: the lipid layer providing insulation and support for axons and neurons in the CNS (the white matter of the CNS).

NBS: newborn screen.

NCS: to evaluate peripheral nerve function; often performed with EMG.

NGS: new, advanced, rapid sequence techniques including gene panel tests, WES, and WGS.

Visual evoked potential: a test for intactness of nerve pathways for vision.

WES: a type of NGS that analyzes all of the exons (coding sequences).

WGS: a type of NGS that analyzes all of the DNA.

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Specific leukodystrophy diseases and their abbreviations are listed in Table 2. UCB, umbilical cord blood; BMT, bone marrow transplant; NGS, next-generation sequencing.

manifestations of systemic illness predominate, even with significant white matter abnormalities in the brain, were also excluded from characterization as leukodystrophies. These, as well as other genetic diseases, such as neuronal ceroid lipofuscinosis and mitochondrial diseases, were termed “genetic leukoencephalopathies.” Although leukoencephalopathies may reveal significant white matter changes in the brain, the predominant symptoms of the disease are considered to arise from the gray matter or other organ systems.

### CLINICAL PRESENTATION

The age of onset of symptoms in leukodystrophies may vary from prenatal to adult. In neonates and infants, presenting symptoms can include encephalopathy or developmental delay. In children, adolescents, and adults, symptoms can be more insidious, ranging from behavioral or psychiatric changes; loss of formerly achieved milestones; or deterioration in skills, vision changes, or ataxia or gait changes (often from spasticity).

Attention-deficit/hyperactivity disorder and other subtle cognitive changes may be the presenting symptoms and often precede motor dysfunction in leukodystrophies with late childhood or juvenile onset.<sup>24</sup> In general, hypomyelinating leukodystrophies present more often with motor delay versus motor regression typically seen in demyelinating leukodystrophies.

Seizures are much more common than previously realized in children with leukodystrophies and affect up to 49% of children with the disease.<sup>2</sup> In rare cases, seizures may be the presenting symptom, such as in Alexander disease. Epilepsy is a common feature of Krabbe disease, megalencephalic leukoencephalopathy with subcortical cysts, sialic acid storage disorders, peroxisomal disorders, and L-2-hydroxyglutaric aciduria.<sup>16</sup>

A few leukodystrophies are more likely to have classic presentations. In a child with acute deterioration of neurologic status, particularly after a febrile illness or head injury, mitochondrial disease or vanishing white matter (VWM) disease are

considerations. Infants with PMD often present at birth or within the first 2 months of life with hypotonia, rotary nystagmus, head titubation, and sometimes stridor attributable to vocal cord paralysis.<sup>25</sup> Macrocephaly is a common feature in megalencephalic leukoencephalopathy with subcortical cysts (MLC), Canavan disease, and Alexander disease, and microcephaly is a feature of Aicardi-Goutières syndrome and RNase T2-deficient leukoencephalopathy.<sup>16</sup> In the neonatal period, Aicardi-Goutières syndrome may often be confused with a congenital cytomegalovirus infection shared symptoms of intracranial calcifications and microcephaly and, in some, hepatosplenomegaly and thrombocytopenia.<sup>26</sup> X-ALD can be considered in a school-aged boy with skin color changes and/or adrenal insufficiency (eg, Addison disease). Children with 4-H syndrome or RNA polymerase III-related leukodystrophies may be identified by their other systemic symptoms including dental abnormalities, progressive myopia (nearsightedness), and hypogonadotropic hypogonadism.<sup>16</sup>

The age of onset of symptoms and/or developmental regression may also help narrow the differential diagnosis. Although most leukodystrophies have both infantile and juvenile or adult forms, one of these groups is typically predominant. The most common forms of Aicardi-Goutières syndrome and PMD display symptoms from birth or within the first few months of life.<sup>25,26</sup> Ninety percent of patients with Krabbe disease are of infantile onset with symptoms presenting between 6 and 12 months of life.<sup>27</sup> The most common form of MLD is the late-infantile form with onset of symptoms between 1 and 2 years of age. Neurologic symptoms in boys with X-ALD occur most often in the elementary school years, between 4 and 10 years of age.

Developmental regression and loss of previously attained milestones can be a presentation of some leukodystrophies and is often the symptom that brings the child to medical attention. In this situation, an urgent evaluation with a pediatric neurologist should be considered.

## MRI AND NEUROIMAGING

An MRI of the brain is the gold standard investigation in a patient with a suspected leukodystrophy or leukoencephalopathy.<sup>16</sup> Although computed tomography (CT) can indicate abnormal signal quality in the CNS myelin, the more detailed signal characteristics of an MRI can provide potentially diagnostic information. Furthermore, MRI is preferable to CT for visualizing abnormal signal and because it involves less radiation exposure. Many publications have identified MRI patterns in leukodystrophies that can be used for diagnosis.<sup>28-33</sup> Key features on MRI include the presence of contrast enhancement, the presence of cysts, calcifications,

or more subtle structural abnormalities.<sup>34</sup> The predominant location, confluent versus multifocal nature of the white matter abnormalities, and signal changes, including hypomyelination versus high T2 signal abnormality and the relative T1 signal hyper- or hypointensity, are the primary discriminating MRI characteristics.<sup>16,28</sup> Although MRI algorithms are helpful for diagnosis,<sup>28</sup> there are limitations on their sensitivity and specificity, and they require skilled radiologic interpretation and experience.<sup>29</sup>

The changing appearance and characteristics of myelin with normal development can also cause complexity in interpreting MRIs.<sup>35</sup> There is a range of normal development of myelin appearance on MRI, and at age 2 years some children will not be fully myelinated. Hypomyelination can also be a result or accompanying feature of other genetic diseases, systemic disorders, or illnesses.<sup>36,37</sup> MRI interpretation is also complicated by normal developmental features: the T1 and T2 signal characteristics of myelin change between birth and 1 year; myelination proceeds from central brain structures to more peripheral white matter and posteriorly to anteriorly. In particular, until the age of 2 years, the CNS of children is normally relatively hypomyelinated compared with adults. Therefore, in a child younger than 1 year with possible hypomyelination, a follow-up MRI of the brain after 24 months, or serial MRIs every 6 to 12 months, is recommended to establish the diagnosis of hypomyelination.<sup>16</sup>

Despite these caveats, some leukodystrophies have key features on MRI, which can suggest a diagnosis for classic presentations (Fig 1, Table 2).<sup>16,38,39</sup> Although not completely sensitive and specific, multiple sclerosis (Fig 1) and other

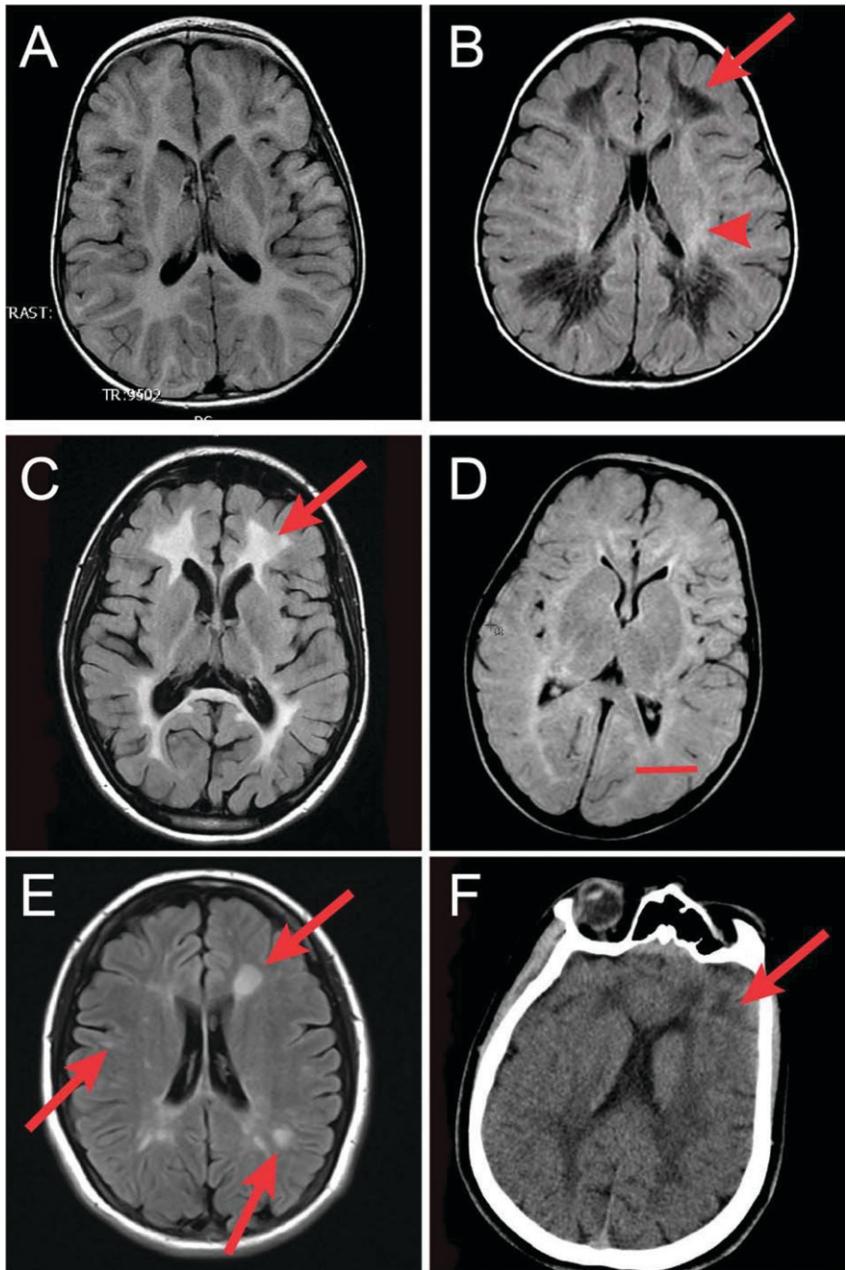
mimicking conditions (such as periventricular leukomalacia from prematurity) typically have different MRI features. Overall, the MRI findings should be interpreted in concert with the findings of the clinical history and physical examination.

## DIAGNOSIS

A genetic diagnosis offers affected families a variety of important options, including disease-specific therapies in some cases and family planning advice in all cases. For a few leukodystrophies, early diagnosis can lead to a halt in disease progression and, in some instances, a cure.

After a diagnosis is suspected on the basis of clinical presentation and MRI findings, biochemical and/or genetic studies are required for a final determination. Depending on available expertise, early referral and involvement of a pediatric neurologist, geneticist, and genetic counselor are important for guiding diagnostic testing, care, and potential further referral (for example, if HSCT is indicated). However, in situations in which timely diagnosis is important, with appropriate guidance, a primary physician can initiate diagnostic tests. Further referral to a clinician or clinical center with expertise in leukodystrophy care can be helpful. For example, online leukodystrophy support groups such as the United Leukodystrophy Foundation or the Leukodystrophy Care Network can direct patients toward centers with leukodystrophy expertise.

Testing of other organ systems may provide additional information to help confirm a diagnosis or differentiate it from others.<sup>40</sup> Possible testing includes an ophthalmologic examination for indications of ocular involvement; electromyography (EMG) to evaluate



**FIGURE 1** Illustrative examples of MRIs of different leukodystrophies and of leukodystrophy mimics. Images are axial slices. A, T2 image of normal brain. B, T2 MRI image of VWM disease; arrow points to hypodense (dark color) white matter; arrowhead points to abnormal hyperintense (bright) white matter. C, T2 image of MLD, with hyperintense (bright) signal in the white matter (arrow). D, T2 image of a hypomyelinating leukodystrophy, PMD, in which the relative paucity of myelin is seen (red line, compare with normal MRI of A). E, T2 image of multiple sclerosis, with scattered areas of hyperintense signal (arrows). F, CT image of VWM disease; abnormal signal in white matter is present (arrow) but is much easier to see on MRI (B).

for myopathies; a nerve conduction study (NCS), which may reveal a peripheral neuropathy; brainstem auditory evoked potential to evaluate for hearing loss; and visual

evoked potentials to examine vision.<sup>40</sup> Lumbar punctures with cerebrospinal fluid (CSF) analysis may show protein elevation in active demyelination or a lactic acid

elevation in mitochondrial disease. CSF leukocytosis and elevated interferon- $\alpha$  and neopterin suggest Aicardi-Goutières syndrome. Lastly, CSF N-acetyl aspartate (NAA) is elevated in Canavan disease.<sup>16</sup>

The Global Leukodystrophy Initiative published a clinical approach to diagnosis of patients with leukodystrophies in 2015. Its approach combines 3 elements: (1) testing for treatable diseases; (2) testing based on MRI features; and (3) next-generation sequencing technologies, particularly gene panel-based approaches and whole-exome sequencing (WES).<sup>16</sup> There is utility in making an expedient diagnosis by excluding treatable forms of leukodystrophies, curtailing other expensive and lengthy testing, and providing valuable reassurance and prognostic information to the patient and family.<sup>16</sup>

Steady advances in next-generation sequencing technologies are making WES a first-tier option for diagnosis of complex genetic disorders with reported yields of 25%.<sup>41</sup> Unbiased genome-wide approaches exemplified by WES or whole-genome sequencing (WGS) provide the potential for diagnosis of known diseases without stepwise ordering of multiple individual tests. Furthermore, genome-wide sequencing can contribute to ongoing discovery of novel disease genes. This testing and assistance with interpretation of results can be facilitated with the help of a geneticist and/or genetic counselor.

Next-generation sequencing technologies provide the potential for unbiased diagnosis of known diseases without individual ordering of multiple individual tests and will contribute to discovery of novel disease genes. However, continued limitations and problems associated with this technology

**TABLE 2** Representative Leukodystrophies: Disease; Gene; Classic Features, Including Age at Onset, Symptoms, and MRI Findings; NBS; and Treatment (ERT, HSCT)

Disease	Gene	Typical Age at Onset	Classic Symptoms	Classic MRI Finding?	NBS?	Treatment?
Aicardi-Goutières	Multiple	Birth to 6 y	Microcephaly, seizures	Calcifications	—	—
Alexander disease	GFAP	Birth to 2 y	Delay, regression	—	—	—
Canavan disease	ASPA	3 mo to 1 y	Delay, macrocephaly	—	—	—
Gaucher disease	GBA	Birth to 6 mo	Seizures, spasticity	—	—	ERT
Krabbe (Globoid cell)	GALC1	2–6 mo	Regression, irritability	—	Yes	HSCT
MLD	ARSA	Birth to adult	Varies	—	—	HSCT
PMD	PLP1	Birth to 6 mo	Hypotonia, nystagmus, titubation	Hypomyelination	—	—
VWM	EIF2B	4 mo to 10 y	Symptoms after minor illness	“Stranding”	—	—
X-ALD	ABCD1	4–10 y	ADHD, school problems, Addison	Contrast enhancement	Yes	HSCT, hormones

ADHD, attention-deficit/hyperactivity disorder; GFAP, glial fibrillary acidic protein; —, not applicable.

include (1) substantial cost (up to \$15 000 to \$20 000), although these numbers are rapidly decreasing; (2) potential for identifying unanticipated disease variants unrelated to the test indication; (3) potential false-negative results because of imperfect exome coverage; and (4) methodologic limitations in the interpretation phase if a clear disease-associated variant is not identified. This fourth problem is significant because of the large number of deleterious gene variants in all humans that could plausibly be related to a phenotype (especially in the CNS), which could yield false-positive associations.

WES continues to become more accessible and may become the method of choice for the diagnosis of leukodystrophies, because it can avoid the diagnostic odyssey faced by many patients.<sup>42,43</sup> Researchers in a recent study used WES on a cohort of 71 patients with persistently unresolved white matter abnormalities with a suspected diagnosis of leukodystrophy or genetic leukoencephalopathy. Diagnostic pathogenic variants were identified in 35% (25 of 71) of patients and potentially pathogenic variants were found in clinically relevant genes in an additional 7% (5 of 71) of cases, giving a total yield of clinical diagnoses in 42% of individuals.<sup>17</sup>

Sequencing is as cost-effective as a brain MRI and, with improved data analysis, will become as rapid. However, even after in-depth biochemical and genetic testing, a portion (around 25% to 40%) of leukodystrophy cases can remain undiagnosed.

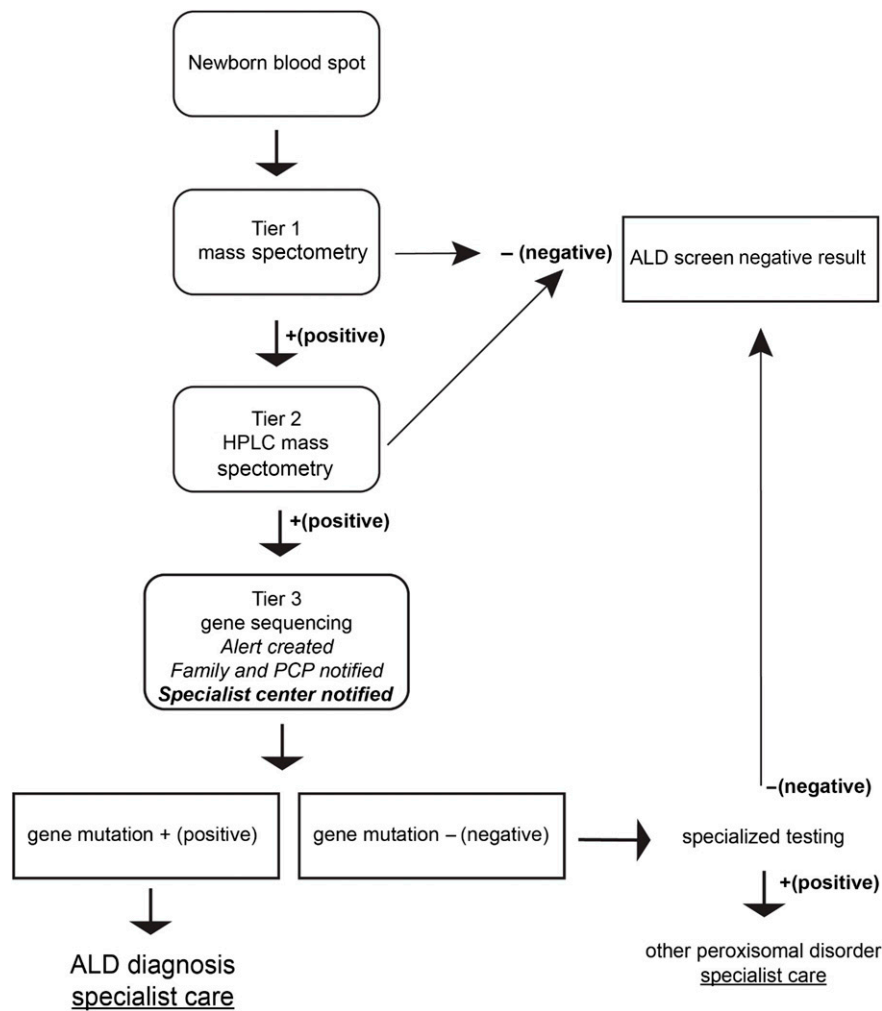
There are important current limitations to use of next-generation sequencing approaches. There are unanswered questions about the disconnect between the underlying gene or biochemical defect, as in X-ALD or Krabbe disease, and actually developing the disease.<sup>44,45</sup> Additionally, WES does have caveats for diagnosis, including copy number variation mutations, mitochondrial genome mutations, and insufficient coverage of some exons to reliably call heterozygous variants. WGS is also becoming clinically available. It provides nearly complete information of DNA sequences but until recently has only been available in research studies. Some recent work suggests that WGS may be useful as a first-line diagnosis tool.<sup>46</sup> However, unresolved ethical questions surround the implementation of WGS as a screening or general diagnostic tool.<sup>47,48</sup> These ethical concerns include that WGS can reveal information unrelated to the patients' current symptoms but that may affect the health of the patient and his or her family, could reveal future health issues before the

patient having decision-making capacity, could affect health insurance coverage, or could reveal unexpected issues such as consanguinity or unexpected parentage.<sup>40</sup>

## NBS

NBS for selected leukodystrophies is being developed in several states.<sup>44,49</sup> X-ALD NBS has been added to the US Health and Human Services RUSP. X-ALD is the only leukodystrophy included (at the time of this publication) on the RUSP. X-ALD is gradually being added to state NBS panels, including (at the time of this publication) 18 states, Puerto Rico, and the District of Columbia.<sup>22,50,51</sup> There are a variety of resources for management of results, and a flow diagram of management for X-ALD (from the California Department of Public Health) is provided in Fig 2.

Krabbe disease has been included in NBS on the basis of legislative mandate in 7 states; Krabbe screening was not recommended by the ACHDNC.<sup>44,49</sup> Addition of conditions outside the ACHDNC process, such as occurred for Krabbe disease, has been controversial. Krabbe disease was proposed for inclusion on the RUSP, but it was not confirmed because of a lack of evidence of an effective treatment. In Krabbe disease, mutational analysis and residual



**FIGURE 2** Simplified protocol for X-ALD NBS protocol (schematized from the California Department of Public Health). HPLC, high-performance liquid chromatography; PCP, primary care provider.

galactosylceramidase enzyme activity have only limited ability to predict age of disease onset and whether disease will occur.<sup>45</sup> In the first 8 years Krabbe disease was included in NBS in New York state, most of the infants judged to be high risk on the basis of screening protocols did not develop the infantile form of the disease and have remained asymptomatic.<sup>52</sup> Therefore, referring all high-risk infants for transplant would expose many of them to unnecessary risk, because HSCT is associated with significant morbidity and mortality. However, efforts are continuing to help identify which patients with Krabbe disease are most at risk, for

example, incorporating measurement of psychosine by using liquid chromatography tandem mass spectrometry as a second-tier test. Psychosine is one of several substrates of the galactosylceramidase enzyme, and its accumulation may cause or contribute to the demyelination and neurodegeneration in patients with Krabbe disease.<sup>53</sup>

Despite the controversies highlighted by NBS for Krabbe disease, as technology advances and new therapies emerge, it is highly likely that other leukodystrophies will be considered for NBS. Factors

affecting recommendation for NBS include variability in disease course, variability in penetrance and disease progression, and limited treatment options.<sup>54–56</sup> Generally, criteria for inclusion in NBS include availability of an appropriate test, a clinical history that includes a potential for impact with early intervention, and an effective therapy. As new therapies become available, additional conditions may become potential targets for NBS implementation. Once NBS is implemented, there is variability in each state as to the testing methodology used, the value or cutoff reported as positive, and means of

confirmatory and secondary testing. Finally, because treatments such as HSCT for Krabbe disease can be expensive or carry risk or have limited efficacy, a decision to implement NBS requires careful consideration of pros, cons, risks, benefits, and costs.<sup>55</sup>

Even for diseases with an available treatment, such as cerebrotendinous xanthomatosis, identifying a testing algorithm with a low false-positive rate and the ability to use existing equipment has been an ongoing area of development.<sup>57,58</sup> Additionally, the cost of test implementation and the development and organization of resources for the evaluation and treatment of identified affected children have been road blocks in NBS for leukodystrophies. Further debate revolves around the potential harm to families of children who have false-positive test results.

Screening for X-ALD is aimed at identifying infants before the onset of neurologic symptoms associated with the cerebral form of the disease, because early treatment with HSCT can prevent severe disability and death. Even for patients who do not develop cerebral disease, early identification can be life-saving by preventing adrenal crisis, because adrenal dysfunction occurs in approximately 90% of patients with X-ALD. For asymptomatic boys in childhood, endocrine monitoring is suggested with an annual clinical evaluation and with serum adrenocorticotropic hormone and cortisol tests every 6 months.

An annual neurologic evaluation is also recommended for X-ALD.<sup>59</sup> Approximately 30% to 40% of patients with X-ALD will go on to develop the cerebral form of the disease.<sup>60,61</sup> Because of the risk of morbidity and mortality with HSCT, boys do not receive transplants unless there is evidence of cerebral

involvement.<sup>59</sup> Protocols have been developed to monitor for cerebral involvement with serial MRIs recommended every 6 months from 1 to 12 years of age. After 12 years of age, MRIs are performed yearly. If an abnormality is detected on MRI, the MRI is scored by using a specialized scoring system (Loes score) to determine if HSCT is appropriate.<sup>58</sup> HSCT is typically considered appropriate if the Loes score is less than 9, with a performance IQ of greater than 80.<sup>59,62</sup> HSCT in children in whom the Loes score is greater than 9 and who have significant neurologic involvement including IQ less than 80 is not recommended because of poor outcomes.

NBS for X-ALD can also identify other peroxisomal disorders such as Zellweger spectrum disorder, acyl-CoA oxidase deficiency, and D-bifunctional protein deficiency. Unfortunately, at this time, only supportive care is available for treatment of these other peroxisomal disorders.<sup>61</sup> As data from the experience of NBS for X-ALD and Krabbe disease from New York state become available, new complications may be identified, but also ways to improve screening, follow-up, and pathways to treatments can be developed.

## TREATMENTS

Curative options for leukodystrophies are disappointingly sparse at the current time. The only option is HSCT. HSCT is only effective for a subset of leukodystrophies, chiefly X-ALD, MLD, and Krabbe disease,<sup>63-65</sup> and is only helpful if transplant is performed before substantial disease progression. However, it is important to note that even in the absence of a curative therapy, treatments, such as for spasticity or feeding problems, can

improve the lives of children with leukodystrophies.

Although not a cure, HSCT can prolong life and preserve cognitive skills when performed in presymptomatic infants with Krabbe disease.<sup>66,67</sup> However, most treated children still experience spasticity, lower-than-average growth, and difficulties in expressive language, adaptive behavior, and motor function.<sup>66,67</sup> Infants receiving a transplant before 30 days of age, most of whom had Krabbe disease diagnosed in utero because of family history, had better survival and functional outcome than those who received transplants later.<sup>68</sup> Presymptomatic transplant is reported to result in normal receptive language,<sup>40</sup> attenuation of symptom severity,<sup>40</sup> and longer survival compared with untreated infantile Krabbe disease. However, most children have progressive gross motor delays ranging from mild spasticity to inability to walk independently, and a few have acquired microcephaly.<sup>40</sup>

A study performed on the outcomes of HSCT in patients with MLD showed that 7 out of 27 patients died of infection, regimen-related toxicity, or disease progression.<sup>69</sup> The researchers found that patients with motor function symptoms at the time of transplant did not improve after transplant. Transplant fails to correct disease in the peripheral nervous system, because enzyme is not delivered to the peripheral nerves, which greatly affected motor development as peripheral neuropathy can be severe as early as 3 month of age.<sup>69</sup> After HSCT, auditory evoked responses, visual evoked potentials, EEG, and/or peripheral nerve conduction velocities stabilized or improved in juvenile patients with MLD but continued to worsen in most patients with the late-infantile



presentation.<sup>69</sup> Lentiviral gene therapy correction of a patient's own bone marrow stem cells (hematopoietic stem cell gene therapy [HSC-GT], in which a normal copy of the gene is delivered by a lentivirus to replace the patient's mutant copy) appears to be well tolerated, including for infantile MLD.<sup>70</sup> Although lentiviral HSC-GT may offer reduced complications and the potential for improved treatment, outcomes data are not yet available.

HSCT is the only effective therapy for cerebral X-ALD that has been proven to date, and it is more likely to be effective if it is performed at an early stage of neurologic involvement with a light burden of disease on MRI. Favorable baseline disease characteristics for HSCT include one or fewer neurologic deficits and a Loes MRI score <9.<sup>62</sup> HLA antigen-matched siblings are also preferred. To determine if HSCT is indicated, presymptomatic boys are monitored with a yearly neurologic examination and with a brain MRI every 6 months from age 2 years to 12 years and then yearly to evaluate for the development of white matter signal abnormalities and contrast enhancement on MRI. HSCT does not prevent the adrenal involvement or the later development of the spinal cord and peripheral neuropathy (adrenomyeloneuropathy).<sup>62</sup>

Autologous, genetically modified HSCT (using lentiviral delivery of a wild-type copy of the gene into the patient's own cells; HSC-GT) has been studied in patients with X-ALD. Clinically, patients developed mild cognitive or functional deficits after treatment, although these stabilized with longitudinal assessments. On MRI, there was resolution of the contrast enhancement. The investigators concluded that this initial trial had outcomes similar to those observed

in standard HSCT with reduced risk of graft-versus-host disease and the potential for improved long-term outcomes.<sup>18</sup>

Patients who undergo HSCT are at high risk for disease progression: first, because there is a time-lag between transplant and effective rescue, and second, because the HSCT process itself appears to accelerate disease progression in some patients. HSCT is not always successful and carries a substantial mortality risk approaching 20%. Donor sources for HSCT include cord blood, bone marrow, or peripheral blood stem cells.<sup>66,71</sup>

Enzyme replacement therapy (ERT) is an option for some of the lysosomal disorders (Gaucher disease, Fabry disease, mucopolysaccharidosis types I, II, and VI, and Pompe disease) which can have leukodystrophy as a component.<sup>71,72</sup> ERT has shown some efficacy in animal models in other leukodystrophies,<sup>73</sup> and clinical trials are being pursued but convincing effectiveness has not yet been shown.

"Lorenzo's oil" is a treatment that has been proposed to reduce progression of X-ALD in its cerebral form.<sup>74</sup> A 4:1 mixture of glyceryl trioleate and glyceryl trierucate, Lorenzo's oil can normalize levels of very-long chain fatty acids in plasma although as previously noted these do not show a correlation with disease progression, and current published data to do not demonstrate efficacy for inhibiting disease progression or altering outcomes.<sup>75-77</sup> In the United States, Lorenzo's oil can be obtained by foreign import via an expanded access program.

Gene therapy is rapidly progressing toward becoming clinically available. Thus far, it has shown

promise in MLD and X-ALD.<sup>78,79</sup> A clinical trial of HSC-GT for the treatment of MLD was initiated in Milan, Italy, in 2010. Results showed reconstitution of arylsulfatase A (ARSA) activity in all hematopoietic lineages and in the CSF. The Gross Motor Function Measurement scores also showed that gross motor performance was similar to that of normally developing children for most of the patients who underwent HSC-GT up to the last follow-up. Initial reports indicate gene therapy may have less morbidity and mortality than HSCT while still being effective in halting disease.<sup>80</sup>

Promising clinical trials are ongoing in the treatment of Aicardi-Goutières syndrome with reverse transcriptase inhibitors.<sup>81</sup> In Alexander disease research, antisense oligonucleotides were used to successfully suppress glial fibrillary acidic protein in mouse models, resulting in improved body condition and rescue of hippocampal neurogenesis.<sup>82</sup> There is significant interest in using stem cells or modified induced pluripotent stem cells for the treatment of leukodystrophies.<sup>83</sup> Although of great potential, practical use still does not seem imminent. Novel drug discovery, or repurposing of known drugs, is another promising avenue of current therapies for several leukodystrophies.<sup>77,84,85</sup> Other possible disease-modifying treatments, such as vitamin D treatment of X-ALD, are also being studied.

Common challenges with rare disease research include the recruitment of adequate numbers of patients, obtaining natural history data, and identifying biomarkers for use in later clinical trials. The clinician plays an important role in helping patients and families with rare diseases connect to research and clinical trials. Although the

Internet and social media have increased awareness of clinical trials and research, clinicians can discuss with families the utility of natural history studies and other research, which may not directly benefit their child but will help children in the future.

### **THE ROLE OF PEDIATRICIANS IN CARE OF PATIENTS WITH LEUKODYSTROPHIES**

Although there are significant limitations in the treatment of leukodystrophies, there are tremendous opportunities for improving the care of patients.<sup>86</sup> It is important to stress that not all leukodystrophies are progressive or worsen with time, an incorrect and formerly commonly held view. A patient-centric approach can prompt and facilitate discussions between the clinician and patient and family about what care and treatment is most important and most helpful. As has been demonstrated for other currently incurable genetic conditions (eg, cystic fibrosis), the strategies of routine symptomatic care can have a profound effect on both the quality and the duration of a patient's life.<sup>87</sup> Nationally and internationally, there is a wide variability in the care and costs of care or treatment of leukodystrophy patients: a greater than sevenfold difference in costs across children's hospitals in the United States.<sup>88</sup>

Complications of disease, even if the disease itself is not progressive, can lead to progressive disability requiring assistance for mobility and activities of daily living as well as surgery.<sup>89,90</sup> Patients with leukodystrophy can have significant health care requirements and costs, driven largely by inpatient admissions.<sup>2,91</sup> As expected, patients who undergo HSCT have much higher costs. However, even taking into account HSCT, patients with

infections and patients needing mechanical ventilation have higher costs and health care needs.<sup>91</sup> Building from this analysis of health care use, a recent study showed that infection rates in patients with leukodystrophy correlate with potentially modifiable risk factors.<sup>20</sup> For example, failure to vaccinate annually against seasonal influenza significantly increases the risk for hospitalization with influenza, and urinary tract infections are associated with the presence of indwelling urinary catheters. Although these issues are common sense, they also outline a path for potential clinical care guidelines that could be implemented at this time to reduce hospitalizations and improve care.

Several organizations have been developed in concert between families, researchers, and clinicians to advance the recognition, diagnosis, treatment, and care of children with leukodystrophies. Preventive and symptomatic care guidelines for patients with leukodystrophies were first published in 2015 by Van Haren et al as part of an effort from the Global Leukodystrophy Initiative.<sup>86</sup> An updated consensus statement was published in 2017.<sup>92</sup> Additionally, guidelines in several areas of care for children with leukodystrophies are under development from the Leukodystrophy Care Network.

Pediatricians play a key role in the care of patients with leukodystrophy by providing an overall view of the patient from a multisystem approach. As possible, referral to a multidisciplinary clinic, as well as use of a team-based approach, offers potential improvement in patient care and facilitates the health care journey experienced by families.<sup>93</sup> Travel to see specialists can be difficult for patients with disabilities, so the local pediatrician becomes

increasingly important for recognizing and preventing complications. Children with leukodystrophies benefit from referrals for occupational, physical, and speech therapy, as well as caregiver instructions for stretching and repositioning. Immunizations should be administered on a standard schedule unless otherwise contraindicated (for example, a patient who is immunosuppressed for a bone marrow transplant). In conjunction with referrals for orthotics and mobility equipment, these measures can have significant effects on the patient's quality of life and prevention of contractures and pressure ulcers.<sup>94</sup> Use of speech augmentative devices and teaching Braille or sign language in children with hearing and vision impairment can also improve quality of life and simplify caregiving.

Monitoring for feeding difficulties can help with the overall health and nutrition of the patient but also prevent complications such as aspiration pneumonia.<sup>94</sup> Constipation is a common complication for children with limited mobility. Medications used to treat spasticity and dystonia may also further compound the problem. Gastrointestinal tract motility may also be impaired and may be related to the brain injury from the disease.<sup>67</sup> Symptoms of constipation in a nonverbal disabled child can include irritability, vomiting, and/or urinary tract infections.

Other potential complications that require monitoring and treatment as the disease progresses include urinary retention, eye dryness and corneal abrasions from decreased blinking, and temperature instability. Irritability can be a presenting symptom of patients with Krabbe disease. Evaluating for the source of pain or discomfort is recommended, including urinary

tract infections, constipation, pressure sores, muscle spasms, and corneal abrasions. Medications such as gabapentin can be used, but nonpharmacologic techniques such as music and repositioning are also encouraged. Peripheral neuropathy can also cause pain in patients with mitochondrial diseases, MLD, and Krabbe disease.<sup>16</sup> Patients with some leukodystrophies including Krabbe disease and Aicardi-Goutières syndrome may develop autonomic instability including periodic fevers not associated with infection or have difficulty maintaining an adequate temperature.<sup>16</sup>

Early referral to specialists, such as pulmonologists, is recommended to help treat sialorrhea, increased lung secretions, and pulmonary insufficiency/weak cough, which can lead to pneumonia.<sup>94</sup> Chest physiotherapy, postural drainage techniques, and home suction machines can help extend life and improve the quality of life. To avoid respiratory infections, an annual influenza vaccination is also recommended.<sup>94</sup> Physiatry and/or orthopedics referral can be considered for spasticity management or monitoring and prevention of complications for hypotonia including scoliosis and hip dysplasia. Endocrinology consultation is necessary for some leukodystrophies such as X-ALD, Aicardi-Goutières syndrome, and 4-H syndrome.<sup>16</sup> Neurology may be involved with the initial evaluation and diagnosis but can also help with ongoing management of neurologic symptoms including seizures, spasticity, and pain and irritability. Palliative care can also be a valuable resource for patients and their families to provide additional support throughout the disease continuum.<sup>95</sup> Where available, pediatric palliative care teams can assist with pain and symptom

management and advance care planning and can help maintain a focus on the child's quality of life. When clinically indicated, palliative care may also include hospice to provide end-of-life care and to ensure the comfort and dignity of children with these terminal illnesses.

An area of treatment that is often forgotten is the mental health of the family and caregivers. The leukodystrophy and its complications puts significant financial, physical, and mental stress on the family. Social workers or case managers can be extremely helpful to families by providing contact information on counselors and psychiatrists, financial services, respite care, and grief counseling. Family disease-specific organizations, local or via the Internet, can also provide resources and support. Importantly, stressors and mental health issues specific to leukodystrophies, as well as common to having a chronic disease, can affect children, adolescents, and adults with leukodystrophies. Mental health supports and services may be necessary for some patients.

### CONCLUSIONS

The field of leukodystrophies has experienced a great expansion in interest and knowledge in the last decade. Collaboration between researchers, clinicians, and patient organizations has helped to organize and focus efforts in patient care and research. Excitement and opportunities have been created by the expanding genetic testing, accelerating gene and disease discovery, improved diagnosis and understanding of the mechanism of disease, and availability of novel treatment options. Leukodystrophies can affect children from all racial, ethnic, and socioeconomic

backgrounds, and recognizing disparities is important to help all children with leukodystrophy receive a diagnosis and appropriate care.<sup>96,97</sup> It remains important to combine this excitement and hope with attention to currently available high-quality clinical care that will greatly improve the lives of patients with leukodystrophy and their families.

### RECOMMENDATIONS FOR PEDIATRICIANS

1. Be aware of leukodystrophies as a disease entity and that treatments are available for some leukodystrophies.
2. Know that treatment of some leukodystrophies is urgent, because the stage of disease may determine the efficacy of treatment.
3. Recognize common presentations for leukodystrophies, including developmental delay or regression in early-onset cases and cognitive changes in older presentations.
4. Recognize disease-specific symptoms that suggest further evaluation, including neurologic deterioration in the setting of a febrile illness or head injury, as in the case of VWM disease and mitochondrial diseases, and skin color changes or Addison disease in a school-aged boy in the case of X-ALD.
5. Be aware that an MRI of the brain is a first step in evaluation for leukodystrophy. There can be characteristic MRI patterns that may help to determine the specific type of leukodystrophy.
6. Recognize the need for partnering with a specialist who is familiar with the diagnosis and care of patients with leukodystrophies, typically a pediatric neurologist and/or geneticist.

7. Ensure that a patient with a newly diagnosed or newly suspected leukodystrophy is referred urgently for diagnosis or has an urgent diagnostic evaluation overseen by a specialist.
8. Know that some leukodystrophies, including X-ALD and Krabbe disease, can be detected by using NBS.
9. Know that it is critical for patients with leukodystrophies to receive standard pediatric care, including immunizations.
10. Recognize that treatment and prevention of disease complications improves the quality of life and longevity of patients with leukodystrophy.

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#### ABBREVIATIONS

ACHDNC: Advisory Committee on Heritable Disorders in Newborns and Children  
CNS: central nervous system  
CSF: cerebrospinal fluid  
CT: computed tomography  
EMG: electromyography  
ERT: enzyme replacement therapy  
HSC-GT: hematopoietic stem cell gene therapy  
HSCT: hematopoietic stem cell transplant  
MLD: metachromatic leukodystrophy  
NBS: newborn screening  
NCS: nerve conduction study  
PMD: Pelizaeus-Merzbacher disease  
RUSP: Recommended Uniform Screening Panel  
VWM: vanishing white matter  
WES: whole-exome sequencing  
WGS: whole-genome sequencing  
X-ALD: X-linked adrenoleukodystrophy

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