Monitoring adrenoleukodystrophy (ALD) and the potential progression to cerebral ALD

Vigilant observation and timely intervention are crucial for improved outcomes

Patients are actor portrayals. Physician is an ALD specialist.
This brochure is for educational purposes only.
Treatment decisions should not be based on such information.

bluebirdbio®

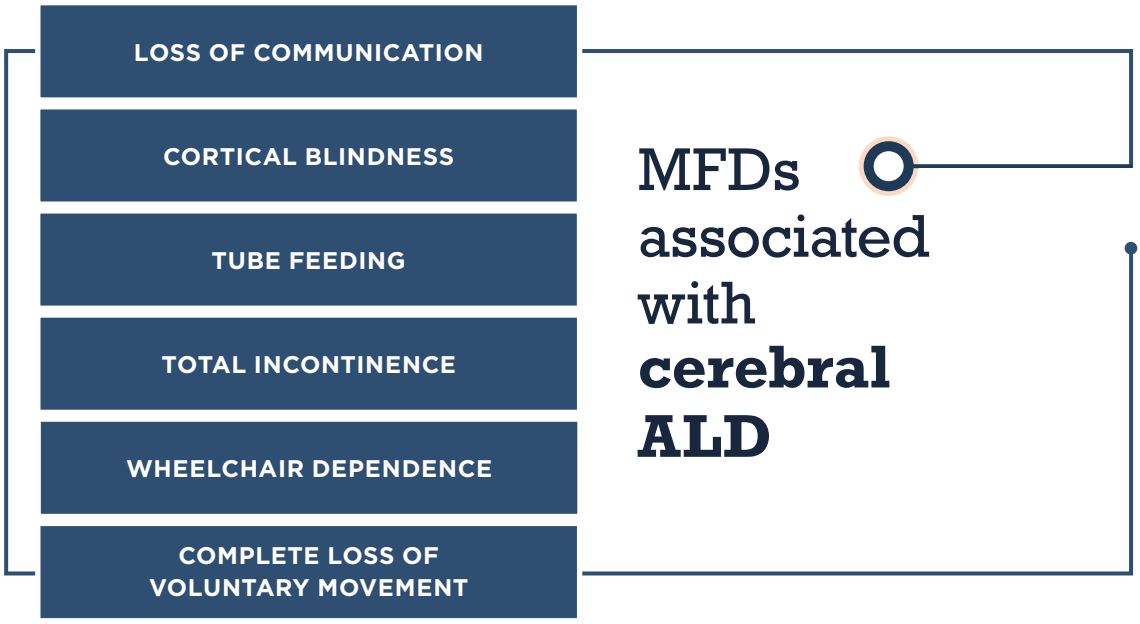
ALD is a rare genetic disease that can progress to life-threatening cerebral ALD[1,2]

Although ALD **affects males more severely**, females may also develop symptoms later in adulthood[3-5]

- ALD is an X-linked disorder that occurs in about 1 out of every 21,000 males[3]
- ALD is caused by mutations in the *ABCD1* gene that result in deficient expression of the peroxisomal ALD protein (ALDP)[1,6]
- Deficient ALDP expression leads to the accumulation of very long-chain fatty acids (VLCFAs) in plasma and tissue—primarily in the nervous system and adrenal glands[6]
- Because ALD is X-linked, it affects males more severely; however, the development of myelopathologic symptoms in women with *ABCD1* mutations is common, with most individuals developing clinical manifestations of the disease by 60 years of age[1,4]

About **40%** of boys with ALD develop cerebral ALD in childhood[2]

- Cerebral ALD, the most severe manifestation of ALD, is characterized by rapidly progressing inflammatory cerebral demyelination and neurodegeneration, which can lead to an irreversible loss of neurologic function and death[7]
- Left untreated, cerebral ALD can lead to a loss of neurologic function, including the development of major functional disabilities (MFDs) and ultimately, death.[7] There are 6 MFDs commonly associated with cerebral ALD that are of particular clinical importance because they severely compromise a patient's ability to function independently. These MFDs are[7-9]:



There is currently **no way to predict** which patients will develop cerebral ALD[1,10]

ALD and cerebral ALD can be challenging to recognize

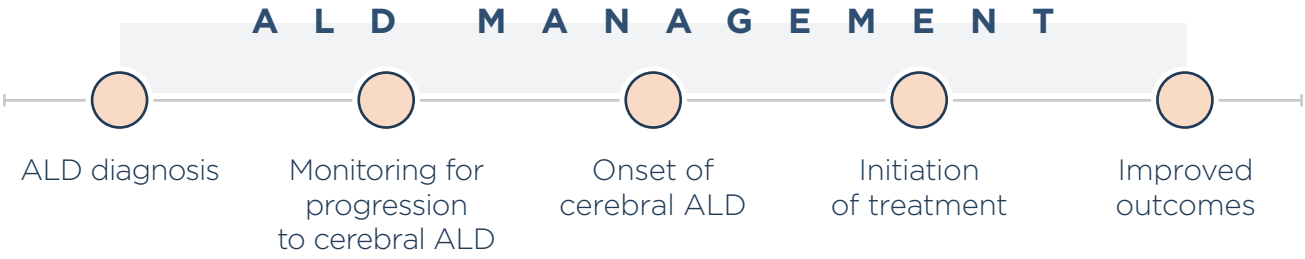
- ALD may be suspected due to any of the following: results from newborn screening (NBS), family history, presentation with adrenal insufficiency of unknown cause, or unexplained progressive cognitive decline or behavioral problems[2,17]
- Symptoms of progression to cerebral ALD may mimic conditions such as attention-deficit/hyperactivity disorder (ADHD), autism, or other home and school problems, which can delay diagnosis[6]

IF ALD IS SUSPECTED, A DIAGNOSIS CAN BE CONFIRMED BY[6]:

- Measuring blood plasma levels of VLCFAs
- Molecular sequencing of the *ABCD1* gene

An early diagnosis of ALD can save lives[11]

Newborn screening provides one of the **earliest opportunities** to diagnose ALD[1,10]



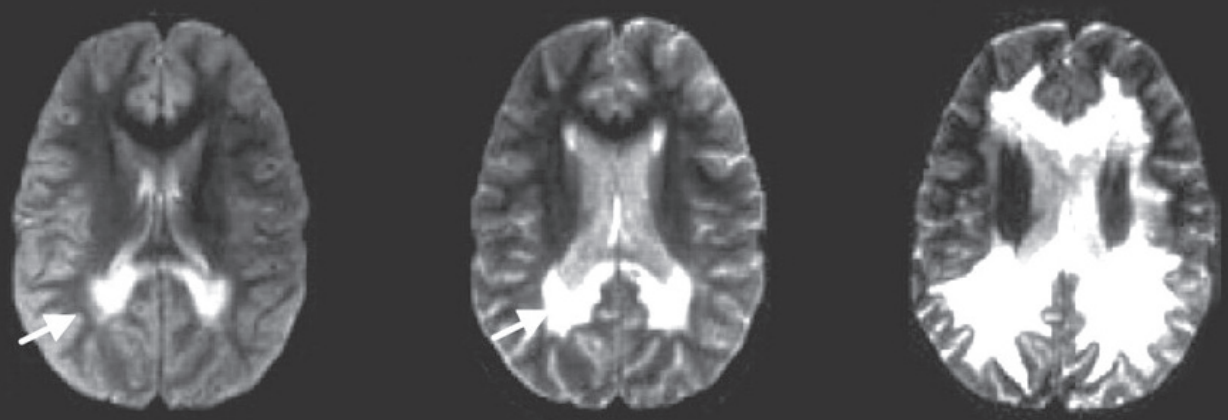
Early diagnosis of cerebral ALD in presymptomatic boys with early radiologic findings is critical because outcomes are better when treatment is performed early in the course of cerebral disease.[7,12-15] **However, only ~50% of cerebral ALD patients are diagnosed in time for effective treatment.**[13,14] NBS allows boys at risk for cerebral ALD to be identified and monitored before the onset of symptoms.[10]

Currently, several US states actively conduct NBS for ALD, with more states set to do so in the future. There are also ongoing pilot NBS programs elsewhere in the world.[10,11] However, NBS is just one of the ways to diagnose ALD—some people are diagnosed through presentation of adrenal symptoms and subsequent testing for VLCFAs in plasma; others are diagnosed through genetic testing because they have a family history of ALD.[3]

Diagnosis of ALD prompts magnetic resonance imaging (MRI) monitoring early enough to detect the brain changes that are indicative of progression to cerebral ALD and to refer the patient for timely treatment **to prevent devastating brain damage**.[16]

MRI screening guidelines for signs of cerebral ALD

Reproduced with permission from Cartier N, Hacein-Bey-Abina S, Bartholomae CC, et al. Hematopoietic stem cell gene therapy with a lentiviral vector in X-linked adrenoleukodystrophy. *Science*. 2009;326(5954):818-823.



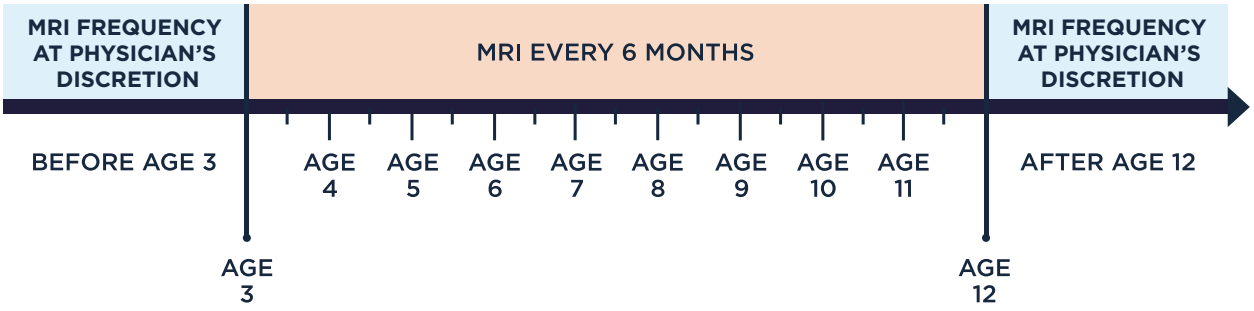
INITIAL SYMPTOMS	MODERATE DISABILITY	MAJOR FUNCTIONAL DISABILITY
• Poor school performance • Behavioral problems • May be misdiagnosed as ADHD	• Hearing • Aphasia/apraxia • Vision impairment • Swallowing dysfunction • Walking/running difficulties • Episodes of incontinence • Seizures	• Cortical blindness • Loss of communication • Tube feeding • Wheelchair dependence • No voluntary movement • Total incontinence

Monitoring ALD with MRI is the only way to detect **progression** to cerebral ALD[2]

Since there is no way to predict which patients with ALD will progress to cerebral ALD, it is important to detect cerebral ALD via MRI as early as possible, as the disease can progress very rapidly.[2,3] Brain changes detected through MRI precede the onset of clinical symptoms of cerebral ALD by months—once these symptoms develop, it is often too late to treat effectively because of the rapid progression of the disease.[16]

According to 2012 guidelines published by Engelen, et al:

MRI SHOULD BE PERFORMED EVERY 6 MONTHS IN 3- TO 12-YEAR-OLD BOYS WITH ALD



According to 2019 guidelines published by Liberato, et al, **if brain MRI shows abnormalities**, applied contrast imaging can further evaluate disease progression and, in particular, active neuroinflammation. If contrast enhancement is not present, MRI should be repeated within 3 months.[16]

> The neurologist at our center is an important part of the team—helping us to interpret the MRI findings, neurological signs, and determining what images are going to identify disease early.

BRADLEY MILLER, MD, PhD
ALD specialist

Although there is no approved treatment for cerebral ALD, allogeneic HSCT is associated with disease stabilization and improved survival

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is currently the only treatment option that can arrest the progression of cerebral ALD and improve survival outcomes.[7]

In a study of patients with both early and advanced cerebral ALD,* treatment in early disease resulted in greater MFD† -free survival (survival without experiencing any MFDs).[7]

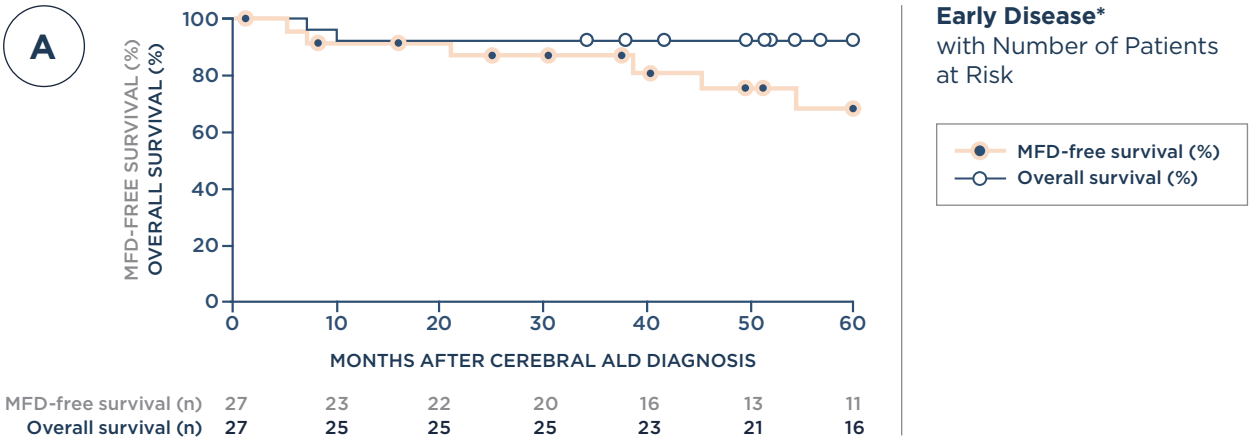
	MFD-FREE SURVIVAL		OVERALL SURVIVAL
	2 YEARS	5 YEARS	
Early Disease* (n=27)	91%	76%	94%
Advanced Disease* (n=10)	20%	10%	90%

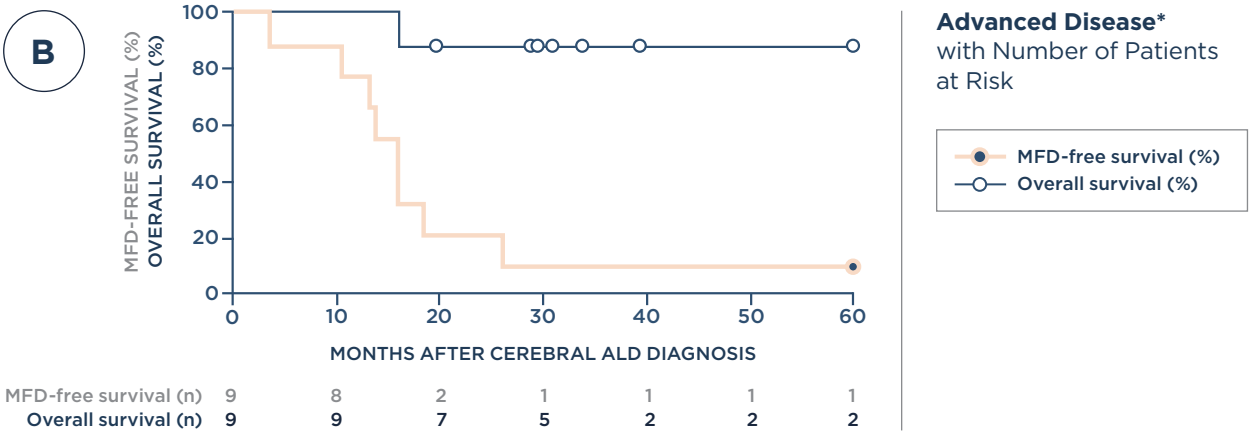
*Early disease: NFS≤1, Loes score 0.5 to ≤9, GdE+; Advanced disease: NFS>1, Loes score >9, GdE+; NFS=neurologic function score: a 25-point score used to evaluate the severity of gross neurologic dysfunction in cerebral ALD by scoring 15 symptoms across 6 categories (hearing, communication, vision, feeding, locomotion, and incontinence); Loes score is a 34-point scale commonly used to quantify the extent of demyelinating brain lesions seen on MRIs in cerebral ALD (higher scores indicate more severe disease); GdE+=positive for gadolinium contrast enhancement, an indicator of active neuroinflammatory disease.

†MFDs: loss of communication, cortical blindness, tube feeding, total incontinence, wheelchair dependence, and complete loss of voluntary movement.

Safety outcomes are typically more favorable if allo-HSCT is performed using cells from a human leukocyte antigen (HLA)–matched sibling donor; however, **less than 30% of patients have a matched sibling donor.**[13]

Outcomes of allo-HSCT vary with clinical stage of disease at the time of transplant and are better in patients who undergo treatment during the early stages of cerebral disease.[7,12-15]





Although allo-HSCT has survival benefits, it also has significant **risks and challenges**[7,13,18]

Allo-HSCT can stabilize disease progression if performed during the early stage of cerebral involvement, but it has significant associated risks. These include transplant-related mortality (TRM), graft failure or rejection, graft-versus-host disease (GVHD), and the potential for opportunistic infections.[7,13,18]

- **100-day TRM rates** of 8% to 12% have been reported
- Engraftment is not a certainty, with **graft failure/rejection rates** ranging from 5% to 18%
- **GVHD rates** have been reported at 18% to 39% for acute GVHD grades 2-4 and 7% to 32% for chronic GVHD
- **Serious infection** following allo-HSCT have been reported in 11% to 29% of patients

Through vigilant monitoring and early diagnosis of cerebral ALD, you can have a positive impact on clinical outcomes

1

IMPLEMENT AN MRI MONITORING PLAN FOR YOUR PATIENT

If monitoring is not part of your normal care routine, refer your patient to an ALD specialist.

2

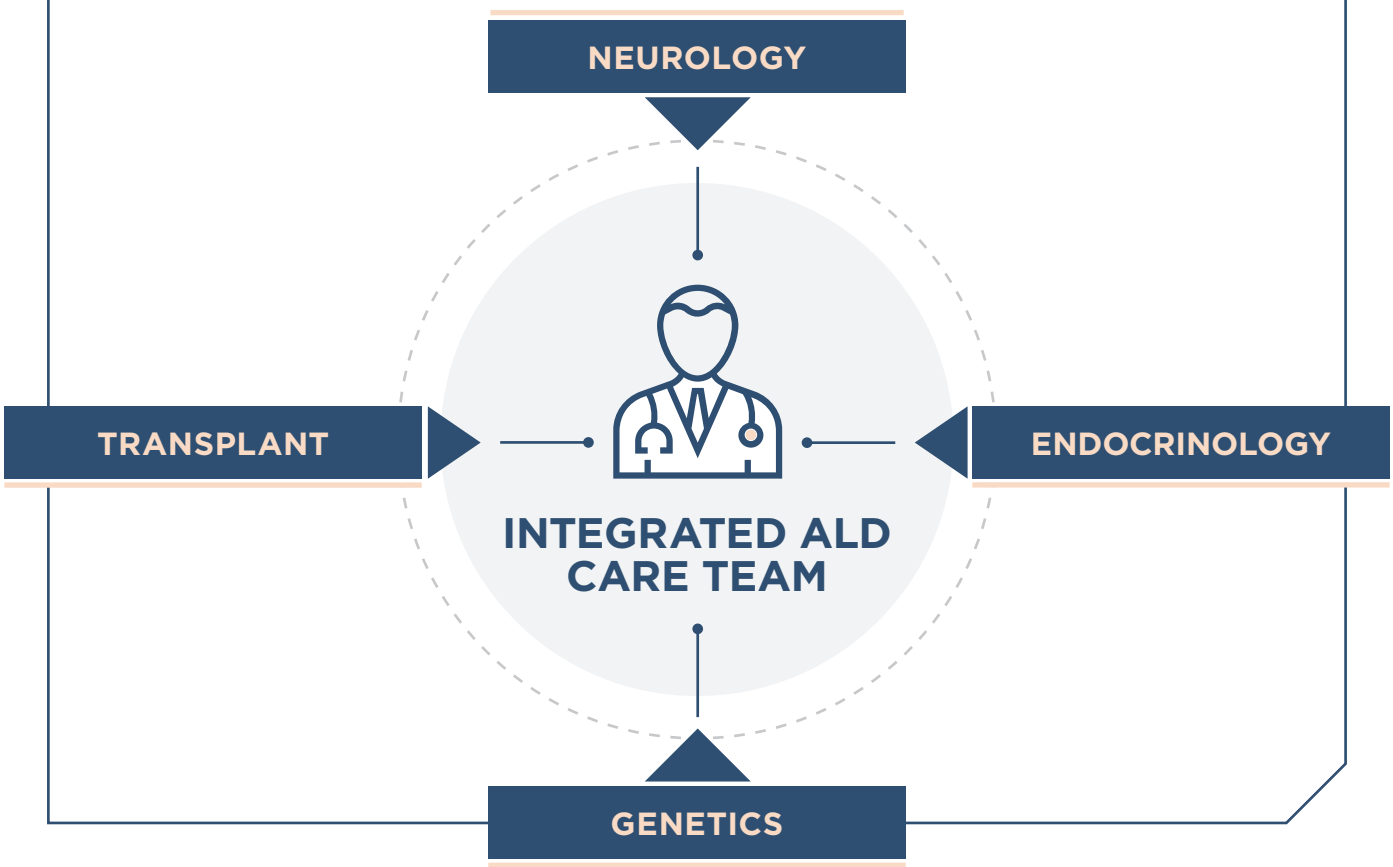
COLLABORATE WITH AN INTEGRATED MULTIDISCIPLINARY ALD HEALTHCARE TEAM

Comprehensive care involves several disciplines.

3

WORK WITH A BONE MARROW TRANSPLANT PHYSICIAN TO PLAN FOR TREATMENT IF NEEDED

Consult with a transplant physician early to ensure timely treatment—results are more favorable the earlier treatment is started.



References:

1. Melhem ER, Loes DJ, Georgiades CS, Raymond GV, Moser HW. X-linked adrenoleukodystrophy: the role of contrast-enhanced MR imaging in predicting disease progression. *AJNR Am J Neuroradiol.* 2000;21(5):839-844.
2. Engelen M, Kemp S, de Visser M, et al. X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. *Orphanet J Rare Dis.* 2012;7:51.
3. Bezman L, Moser AB, Raymond GV, et al. Adrenoleukodystrophy: incidence, new mutation rate, and results of extended family screening. *Ann Neurol.* 2001;49(4):512-517.
4. Engelen M, Barbier M, Dijkstra IM, et al. X-linked adrenoleukodystrophy in women: a cross-sectional cohort study. *Brain.* 2014;137:693-706.
5. Huffnagel IC, Dijkgraaf MGW, Janssens GE, et al. Disease progression in women with X-linked adrenoleukodystrophy is slow. *Orphanet J Rare Dis.* 2019;14(1):30.
6. Kemp S, Huffnagel IC, Linthorst GE, Wanders RJ, Engelen M. Adrenoleukodystrophy - neuroendocrine pathogenesis and redefinition of natural history. *Nat Rev Endocrinol.* 2016;12(10):606-615.
7. Raymond GV, Aubourg P, Paker A, et al. Survival and functional outcomes in boys with cerebral adrenoleukodystrophy with and without hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2019;25(3):538-548.
8. Eichler F, Duncan C, Musolino PL, et al. Hematopoietic stem-cell gene therapy for cerebral adrenoleukodystrophy. *N Engl J Med.* 2017;377(17):1630-1638.
9. Miller W. Stem cell-transplantation therapy for adrenoleukodystrophy: current perspectives. *J Neurorestoratology.* 2017;5:5-19.
10. Kemper AR, Brosco J, Comeau AM, et al. Newborn screening for X-linked adrenoleukodystrophy: evidence summary and advisory committee recommendation. *Genet Med.* 2017;19(1):121-126.
11. Moser AB, Fatemi A. Newborn screening and emerging therapies for X-linked adrenoleukodystrophy. *JAMA Neurol.* 2018;75(10):1175-1176.
12. Peters C, Charnas LR, Tan Y, et al. Cerebral X-linked adrenoleukodystrophy: the international hematopoietic cell transplantation experience from 1982 to 1999. *Blood.* 2004;104(3):881-888.
13. Miller WP, Rothman SM, Nascene D, et al. Outcomes after allogeneic hematopoietic cell transplantation for childhood cerebral adrenoleukodystrophy: the largest single-institution cohort report. *Blood.* 2011;118(7):1971-1978.
14. Mahmood A, Raymond GV, Dubey P, Peters C, Moser HW. Survival analysis of haematopoietic cell transplantation for childhood cerebral X-linked adrenoleukodystrophy: a comparison study. *Lancet Neurol.* 2007;6(8):687-692.
15. Polgreen LE, Chahla S, Miller W, et al. Early diagnosis of cerebral X-linked adrenoleukodystrophy in boys with Addison's disease improves survival and neurological outcomes. *Eur J Pediatr.* 2011;170(8):1049-1054.
16. Liberato AP, Mallack EJ, Aziz-Bose R, et al. MRI brain lesions in asymptomatic boys with X-linked adrenoleukodystrophy. *Neurology.* 2019;92(15):e1698-e1708.
17. Laureti S, Casucci G, Santeusanio F, Angeletti G, Aubourg P, Brunetti P. X-linked adrenoleukodystrophy is a frequent cause of idiopathic Addisons disease in young adult male patients. *J Clin Endocrinol Metab.* 1996;81(2):470-474.
18. Mitchell R, Nivison-Smith I, Anazodo A, et al. Outcomes of haematopoietic stem cell transplantation for inherited metabolic disorders: a report from the Australian and New Zealand Children's Haematology Oncology Group and the Australasian Bone Marrow Transplant Recipient Registry. *Pediatr Transplant.* 2013;17(6):582-588.

"Monitoring for brain changes related to ALD involves an MRI about every 6 months through the critical window when they are at the highest likelihood of cerebral progression—this is crucial because identifying changes early can help us provide treatment."

BRADLEY MILLER, MD, PhD
ALD specialist

Neurologists play a crucial role in the ALD multidisciplinary care team, often ensuring that vigilant monitoring results in timely treatment for cerebral ALD.

VISIT **ItMightBeALD.com** TO LEARN MORE.

bluebirdbio®