MLD is rare and progressive if left untreated[1]

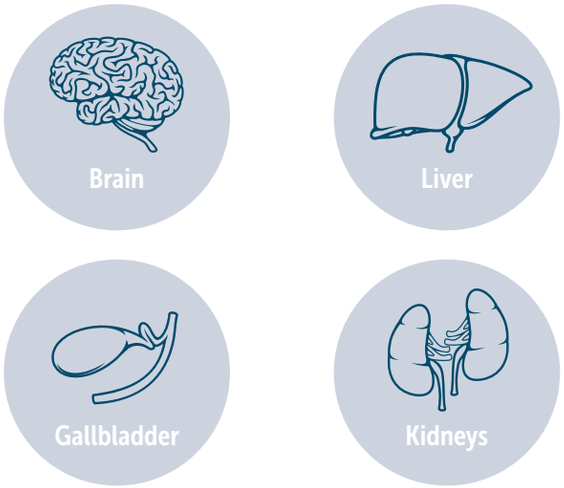
Early diagnosis is the first line of defense against the impacts of metachromatic leukodystrophy (MLD)[2,3]

What is MLD?

- Metachromatic leukodystrophy (MLD) is a rare and life-threatening inherited disease of the body's neurometabolic system[1,4]
- An autosomal recessive disease and a lysosomal storage disorder, MLD is fatal if left untreated[1,4]

Lysosomal storage disorders come in many forms and cause toxic materials to build up in cells[5]

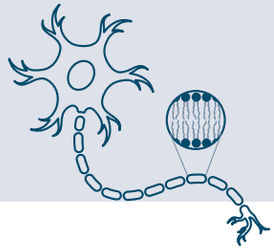
Caused by a pathogenic variant in the *arylsulfatase A* (*ARSA*) gene, MLD results in the accumulation of sulfatides in various tissue types[2,4,6]:



- It is thought that this missing enzyme causes the breakdown of the myelin sheath and damages nerve fibers[4,7]
- There are nearly 50 lysosomal storage disorders that affect different parts of the body, including the skeleton, brain, skin, heart, and central nervous system[5]
- New lysosomal storage disorders continue to be identified[5]

The role of ARSA enzyme within the body

PHYSIOLOGIC



Sulfatides are a major component of the myelin membrane[8]

The **ARSA enzyme** usually breaks down sulfatides in the lysosome[7]

PATHOLOGIC

Mutations in the ***ARSA* gene** cause deficiency of the ARSA enzyme reducing sulfatide breakdown[1,6]

Sulfatide accumulation leads to demyelination and neurodegeneration[1,6]

MLD mainly affects children and has several subtypes[2-4,9]

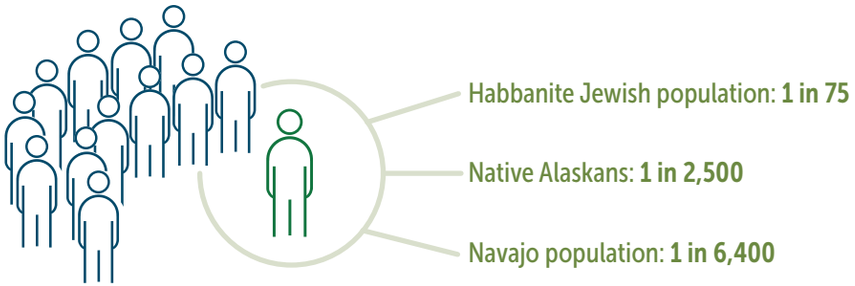
		Early Onset (<7 years)		Late Onset (≥7 years)	
		Late infantile	Juvenile		Adult
			Early juvenile	Late juvenile	
	Distribution	~55%	~15%*	~15%*	~15%
	Age at symptom onset	≤30 months	30 months to <7 years	7 to <17 years	≥17 years
From Symptom Onset	Median survival probability†	2.7 years	9 years		25 years
	5-year survival probability†	25.1%	70.3%		87.1%
	10-year survival probability†	0%	44.3%		69.6%
	Mean age at death†	4.2 years	17.4 years		43.1 years

*Assuming even distribution between early juvenile and late juvenile.[9]
†Based on a systematic literature review of reports from 1921-2006; survival probability as a function of years since onset of symptoms.[4]

How rare is MLD? Who does it affect?

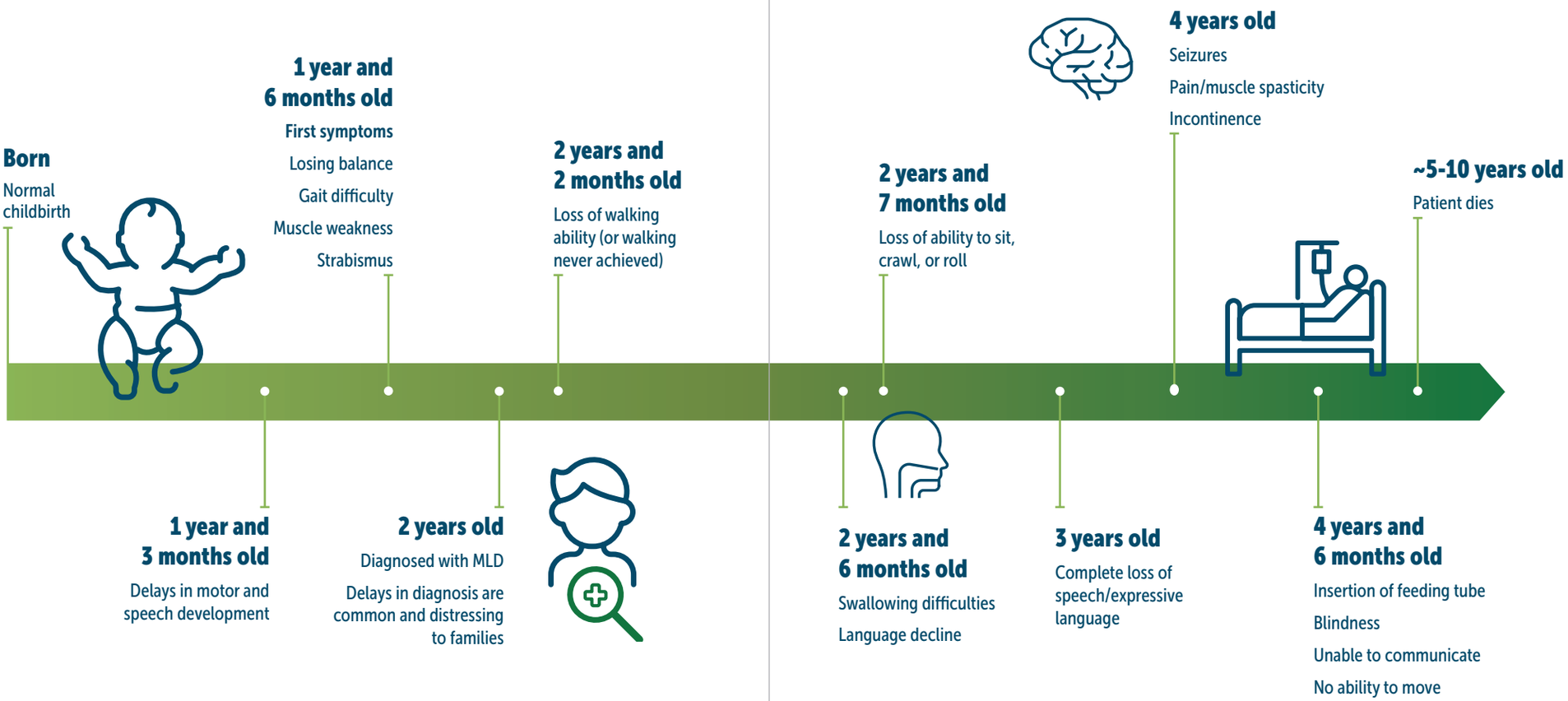
- With improvements in identification technology and awareness, incidence may prove to be higher[11]

These ethnic populations show significantly higher incidence rates[2]



How MLD rapidly progresses, heightening the urgency for early diagnosis[2,12]

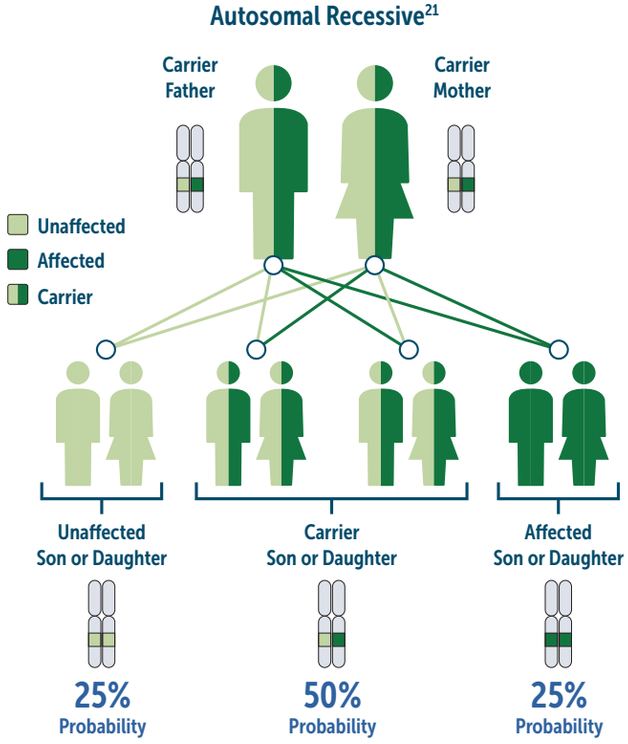
Timeline for the disease course of LI* MLD, the most common form of MLD[2,4,6,9,12-19]



LI, late infantile.
*Disease timeline is representative and based on median age at event from natural history studies or estimated age from caregiver surveys.

MLD is a genetic disease and newborn screening for MLD is not available in the majority of the US.[3,20]

Therefore family screening is critical, and siblings of patients with MLD must be tested.[3]



The life expectancy for those with MLD is tragically short[4]

An estimated **50%** **of children with LI MLD**, the most aggressive form of MLD, die within 5 years of disease onset[22]

1 in 100 **people are carriers** of the *ARSA* mutation that can cause MLD[23]

Over time, the nervous system is damaged and patients with MLD experience neurological symptoms such as: motor problems, behavioral issues, cognitive regression, severe spasticity, and seizures.[6]

- Patients find it increasingly difficult to move, talk, swallow, eat, and see[6]
- Most children with the infantile form die by age 5[22]
- In the juvenile form, death occurs 10 to 20 years following onset[2]

Be on the lookout for symptoms of MLD

Early diagnosis is important, since symptoms can be difficult to identify, and the disease progresses rapidly.[1-3,6,12]

MLD patients appear healthy at birth, but with rapid progression of the disease early testing and treatment are critical.[1-3,6,12]

Healthcare professionals must be equipped with the knowledge to identify early signs of MLD to initiate treatment

Early diagnosis and family screening for MLD are crucial[3]

What are the keys to diagnosing?

✓ **Look closely** ✓ **Act quickly**

- Watch for the early behavioral and cognitive signs of early onset MLD[6]
- When a child who once walked now crawls, when a child who once talked now can't, it may be a sign[4]
- With MLD, a missed milestone may be a red flag and a signal to test promptly[3,12]

Be vigilant for the early signs of MLD

Early Onset (<7 years)[3]

Subtype	Late infantile		Early juvenile	
First signs and symptoms[2,6,9,19,24,25]	• Developmental delay/regression • Peripheral neuropathy • Muscle weakness	• Unsteady gait/toe walking/frequent falls • Hypotonia/arreflexia • Strabismus/ nystagmus	• Educational and behavioral difficulties • Gait disturbance/ falling/poor balance	• Fine motor/ coordination issues • Loss of sphincter control
Examples of caregiver language[24]	• Delayed/never walked • Unsteady/sluggish gait • Lose balance, many falls	• Tremors, shaking • Crying, fatigue • Sudden squint	• Loss of balance, unstable walking • Hand tremors/arm movement as if after a stroke • Difficulty learning, forgetful, lack of concentration	• Personality changes, impulsive, issues with sleep • Peeing pants in school

Late Onset (≥7 years)[3]

Subtype	Late juvenile		Adult	
First signs and symptoms[6,9,14,19]	• Poor school performance • Emotional and behavioral difficulties	• Cognitive and language regression • Social withdrawal	• Behavioral changes • Cognitive difficulties/ disorganized thinking • Decline in school/ job performance	• Psychiatric symptoms, hallucinations • Seizures • Loss of sphincter control
Examples of caregiver language[24]	• Loss of balance, unstable walking • Hand tremors/arm movement as if after a stroke • Difficulty learning, forgetful, lack of concentration	• Personality changes, impulsive, issues with sleep • Peeing pants in school		

If MLD is suspected, pursue confirmatory laboratory testing immediately

Biochemical testing can reveal the presence of MLD[2]

- Urine sulfatide testing and ARSA enzyme activity testing[2]

Genetic testing can confirm the diagnosis[2]

- Gene sequencing for *ARSA* gene variant[2]
- MLD can be detected through an ARSA leukocytes panel[26]

When MLD is diagnosed there isn't a moment to lose

Refer your patient to a specialized treatment center familiar with the treatment of MLD

For more information on a treatment option, or to help your patients locate a treatment center, use this QR code »

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