Metachromatic Leukodystrophy (MLD)

Atidarsagene autotemcel (Lenmeldy™) & Newborn Screening

Metachromatic Leukodystrophy (MLD)

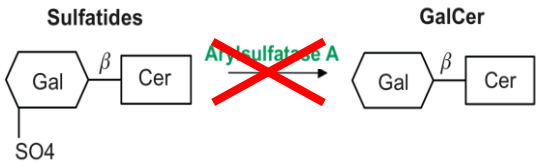
Clinical case definition, estimated prevalence, typical age of diagnosis & diagnostic odyssey

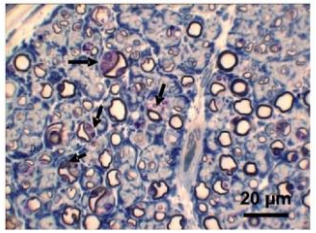
MLD: Metachromatic Leukodystrophy Overview

Metachromatic Leukodystrophy (MLD)

- MLD is a rare, autosomal recessive lysosomal storage disorder, caused by a deficiency of arylsulfatase A (ARSA) enzyme.[1-4]
- Deficiency of ARSA enzyme activity leads to accumulation of sulfatides in the CNS and PNS.[1-4]
- This leads to progressive loss of motor and cognitive skills, dysphagia, seizures, severe neurological disability, and ultimately death. [1-4]

Pathogenic *ARSA* gene variant › **Functional deficiency of ARSA (lysosomal enzyme)** › **Intra-lysosomal sulfatide accumulation** › **Progressive demyelination & neurodegeneration** › **Severe motor and cognitive impairment & death**





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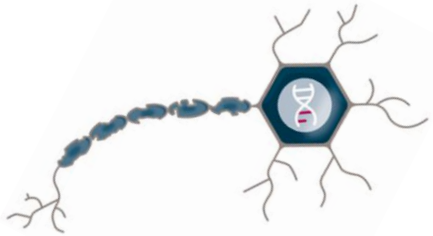

MLD is one of the most common forms of leukodystrophy leading to severe disability and premature death

CNS, Central Nervous System, PNS, Peripheral Nervous System.
*Photo sourced from Figure 1A, Dali CÍ et al, Ann Clin Transl Neurol. 2015 May;2(5):518-33., under CC BY-NC-ND 4.0
1. Wang R et al. Genet Med. 2011;13(5):457-484. 2. Gieselmann V, Krageloh-Mann I. *Neuropediatrics* 2010;41(1):1-6. 3. von Figura K, Gieselmann V, Jaeken J. Metachromatic leukodystrophy. In:. The metabolic and molecular bases of inherited disease, Vol 3, 8th ed. McGraw Hill, 2001:3695,. 4. Gomez-Ospina N. Arylsulfatase A Deficiency. In: GeneReviews®. Seattle (WA): May 30, 2006.[Updated 2020 Apr 30]

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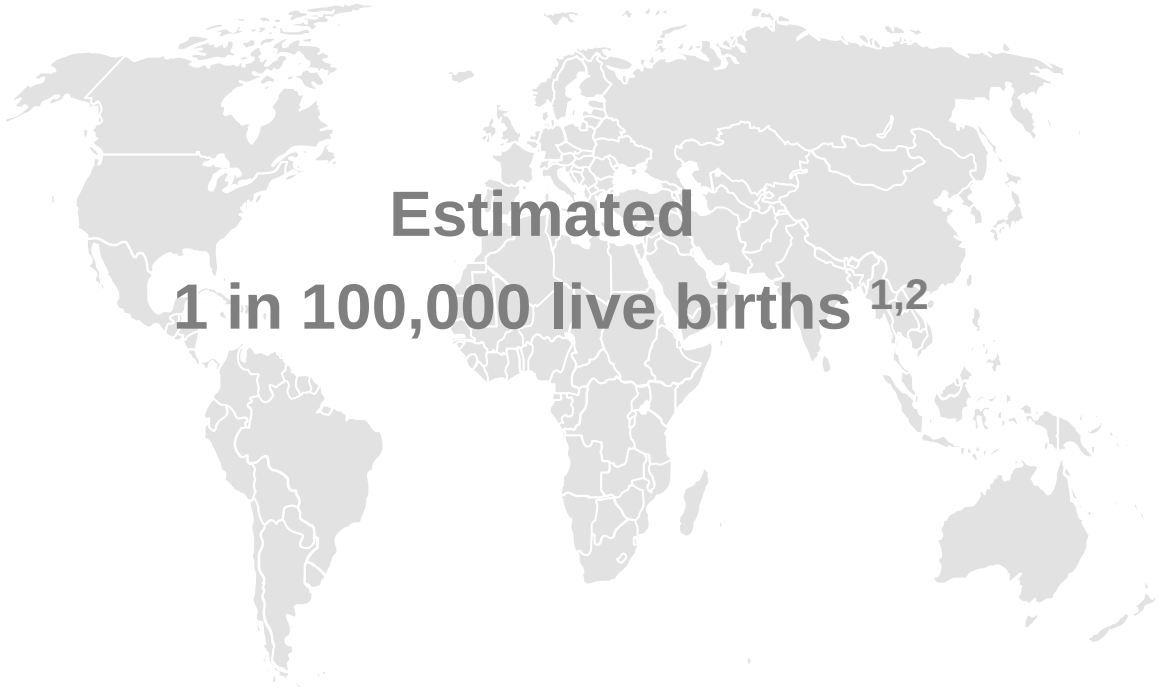
MLD: Overall Incidence and Prevalence

MLD Global Incidence



Overall Incidence of MLD

- **Estimated to be approximately 1 / 100,000 live births** [1-2]
- Ranges from 1 / 40,000 to 1 / 170,000 live births in various countries [3-6]

Overall Prevalence of MLD

- Estimated prevalent population of persons living with MLD globally has not been published in the literature

Certain small isolated communities are thought to have a higher incidence [7-10]

Gieselmann V, Krageloh-Mann I. Neuropediatrics. 2010;41(1):1-6. 2. Soderholm HE et al. Pediatr Neurol. 2020;111:66-69.. 3. Gustavson KH, Hagberg B. Acta Paediatr Scand. 1971;60(5):585-590. 4. Farrell DF. Hum Genet. 1981;59(2):129-134. 5. Heim P et al. Am J Med Genet. 1997;71(4):475-478. 6. Poorthuis BJ, et al. Hum Genet. 1999;105(1-2):151-156. 7. Zlotogora J et al Am J Hum Genet 32:663 -669, 1980. 8. Holve S, Hu D, McCandless SE. Am J Med Genet. 2001;101(3):203-208. 9. Pastor-Soler NM et al. J Inherit Metab Dis. 1995;18(3):326-332. 10. Heinisch U et al. Am J Hum Genet 1995;56(1):51-57

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MLD: Disease Subtype Classification

MLD Clinical Subtypes[1-6]

	Early Onset (< 7 years)		Late Onset (≥ 7 years)	
Subtype	**Late-infantile (LI)**	**Early Juvenile (EJ)**	**Late Juvenile (LJ)**	**Adult**
Age of Onset	< 30 mo	> 30 mo to < 7 yrs	7 yrs to < 17 yrs	≥ 17 yrs
Genotype	Typically 0/0	Typically 0/R	Typically R/R	
ARSA Activity				

Estimated residual ARSA enzyme activity *in vivo*

[a] For the listed genotypes, “0” indicates a null allele and “R” indicates an allele in which some degree of residual enzymatic activity is maintained.

MLD can be classified into clinical subtypes based on the age / expected age of symptom onset
Increasing residual ARSA activity generally leads to later symptom onset
The majority of MLD patients have the early onset subtype

1. Gieselmann V, Krägeloh-Mann I. Neuropediatrics 2010; 41: 1– 6. 2 Wang et al. Genet Med. 2011;13(5):457-484. 4. Biffi et al. Clin Genet. 2008;74(4):349-57 5. Kehrer et al. Neurology. 2021;96(2):e255-e266. 6. Fumagalli et al. J Inherit Metab Dis. 2021;44(5):1151-1164.

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Diagnosing MLD Without Newborn Screening

- A patient with **clinical symptoms** of progressive neurological dysfunction suggestive of MLD typically receives the following diagnostic tests to confirm the diagnosis:
  - ***Leukocyte ARSA activity**** *showing decreased ARSA enzyme activity*
  - ***Urine sulfatides*** *showing abnormally high sulfatide concentration*
  - ***Molecular genetic testing*** *to identify biallelic pathogenic ARSA variants and rule out PSAP/SUMF1 variants*

- ***Decreased enzyme activity alone does not confirm a diagnosis of metachromatic leukodystrophy due to an ARSA enzyme pseudodeficiency that may be present in healthy individuals

Laugwitz, L., Schoenmakers, D. H., Adang, L. A., Beck-Woedl, S., Bergner, C., Bernard, G., ... & Groeschel, S. (2024). Newborn screening in metachromatic leukodystrophy–European consensus-based recommendations on clinical management. European journal of paediatric neurology, 49, 141-154.

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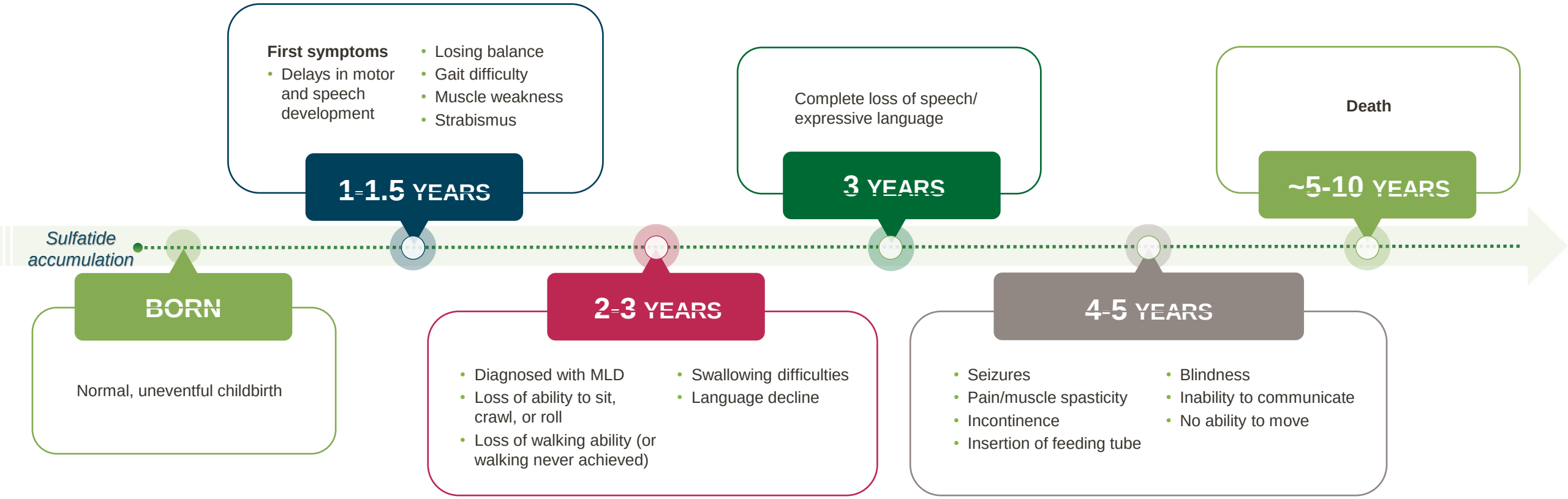
Children with LI MLD experience severe disease burden and early death[1-8]

Patients require significant levels of multidisciplinary care in the absence of disease-modifying therapy



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

LI, late infantile; MLD, metachromatic leukodystrophy.

1. Kehrer C et al. *Neurology.* 2021;96(2):e255-e266. 2. Fumagalli F et al. *J Inherit Metab Dis.* 2021;44(5):1151-1164. 3. Kehrer C et al. *Orphanet J Rare Dis.* 2014;9:18. 4. Harrington M et al. *Orphanet J Rare Dis.* 2019;14(1):89. 5. von Figura K, Gieselmann V, Jaeken J. Metachromatic leukodystrophy. In: *The Metabolic and Molecular Bases of Inherited Disease*, Vol 3. 8th ed. McGraw Hill, 2001:3695-724. 6. Kehrer C, et al. *Dev Med Child Neurol.* 2011;53(2):156-160. 7. Adang L et al. *J Inherit Metab Dis.* 2022;45(S1):293. 8. Ammann-Schnell L et al. *Orphanet J Rare Dis.* 2021;16(1):211.

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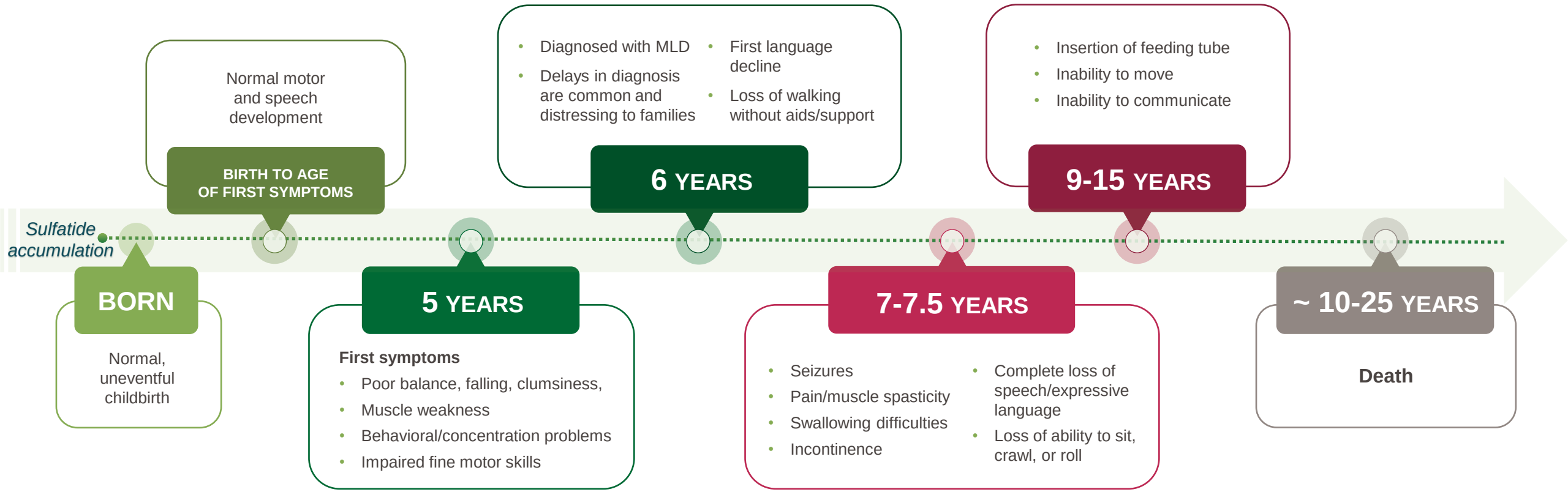
Children with EJ MLD experience severe disease burden and survive for many years in a debilitated state[1-8]

Patients require significant levels of multidisciplinary care in the absence of disease-modifying therapy



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

EJ, early juvenile; MLD, metachromatic leukodystrophy.

1. Kehrer C et al. *Neurology.* 2021;96(2):e255-e266. 2. Fumagalli F et al. *J Inherit Metab Dis.* 2021;44(5):1151-1164. 3. Kehrer C et al. *Orphanet J Rare Dis.* 2014;9:18. 4. Harrington M et al. *Orphanet J Rare Dis.* 2019;14(1):89. 5. von Figura K, Gieselmann V, Jaeken J. Metachromatic leukodystrophy. In: *The Metabolic and Molecular Bases of Inherited Disease*, Vol 3, 8th ed. McGraw Hill, 2001:3695-724. 6. Kehrer C et al. *Dev Med Child Neurol.* 2011;53(2):156-160. 7. Adang L et al. *J Inherit Metab Dis.* 2022;45(S1):293. 8. Ammann-Schnell L et al. *Orphanet J Rare Dis.* 2021;16(1):211.

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Treatment guidelines and current outcomes for MLD

Early-onset MLD: Symptom Management

- In the absence of disease-modifying therapy, palliative care is:
  - Standard of care (SOC)
  - Requires broad multi-disciplinary clinical care teams [5-7]
- Allogeneic HSCT is:
  - Not effective in early-onset MLD
  - Does not represent SOC in early-onset MLD [1-4]

Issue / Symptom	Supportive Care / Management
Declining Mobility	• Physical Therapy, Mobility Aids, Anti-spasticity medications
Respiratory Issues	• Management of pulmonary infections
Immobility / Incontinence	• Personal Nursing Care
Dysphagia / GI issues	• Feeding tubes / suction, nutritional management
Seizures / contractures	• Antiepileptics, muscle relaxants
Loss of sight, hearing, communication	• Family communication support
Mental Health Issues	• Family / psychological counseling

HSCT, hematopoietic stem cell transplant; MLD, metachromatic leukodystrophy.

1. Wang RY et al. Genet Med 2011;13(5):457–84; 2. Kanate 2020 3. Tan 2019 ; 4. MLD EL-PFDD Summary 5. Gomez-Ospina N. Arylsulfatase A deficiency. In: GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2020. 7. Bonkowsky 2021 7. Keller 2021

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Atidarsagene autotemcel (LENMELDY, arsa-cel)

- **INDICATION**
  - Arsa-cel is an autologous hematopoietic stem cell-based gene therapy indicated for the treatment of children with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ), or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD).

- FDA-approved treatment for your individuals with early onset* metachromatic leukodystrophy (MLD).[1-3]

*See full indication.

References: 1. Lamichhane A, Cabrero RF. In: *StatPearls*. NCBI Bookshelf version. StatPearls Publishing; January 2024. Accessed April 30, 2024. https://www.ncbi.nlm.nih.gov/books/NBK560744/ **2.** LENMELDY (atidarsagene autotemcel) Prescribing Information. Orchard Therapeutics. **3.** Orchard Therapeutics. Orchard Therapeutics receives FDA approval of Lenmeldy™ (atidarsagene autotemcel), the only therapy for eligible children with early-onset metachromatic leukodystrophy in the U.S. [press release]. Accessed May 8, 2024. https://ir.orchard-tx.com/news-releases/news-release-details/orchard-therapeutics-receives-fda-approval-lenmeldytm

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Arsa-cel Patient Journey

Pre-Collection Activities:
- Confirm clinical eligibility
- Biological screening

Inpatient Admission to Treatment Center – Trip 1

Mobilized Peripheral Blood Collection:
- Pre-mobilization assessment
- Mobilization of HSPCs
- Possibility of 1-2 leukapheresis

5-7 days

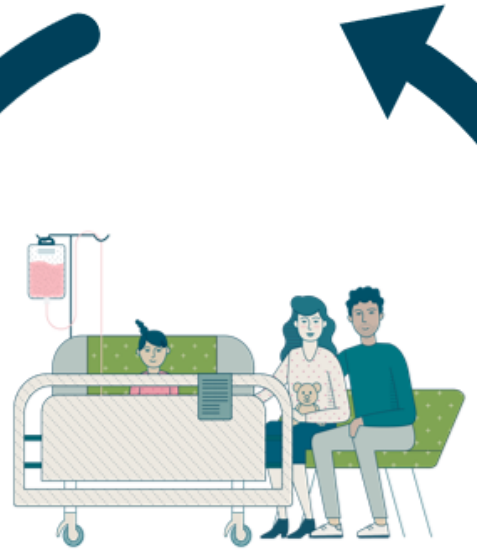
Patient Returns Home

Cellular Source Material Shipping

Drug Product Manufacturing:
- Selection of CD34+ HSCPs
- Ex vivo transduction with LVV
- Cryopreservation of drug product
- Quality control and release testing

40-42 days

Drug Product Shipping



Outpatient Monitoring:
- QTC monitoring following discharge
- Local HCP monitoring

Patient Returns Home

4-8 weeks

Inpatient Recovery Observation
- Monitor drug product engraftment
- Monitor reconstitution

1 day

Administration:
- Thawing of drug product
- Infusion of drug product

4-6 days

Myeloablative Conditioning:
- Infusion of conditioning regimen
- Day of rest

Inpatient Admission to Treatment Center – Trip 2

HCP, healthcare professional; HSPC, hematopoietic stem and progenitor cells; LVV, lentiviral vector.

Reference: LENMELDY (atidarsagene autotemcel) Prescribing Information. Orchard Therapeutics.

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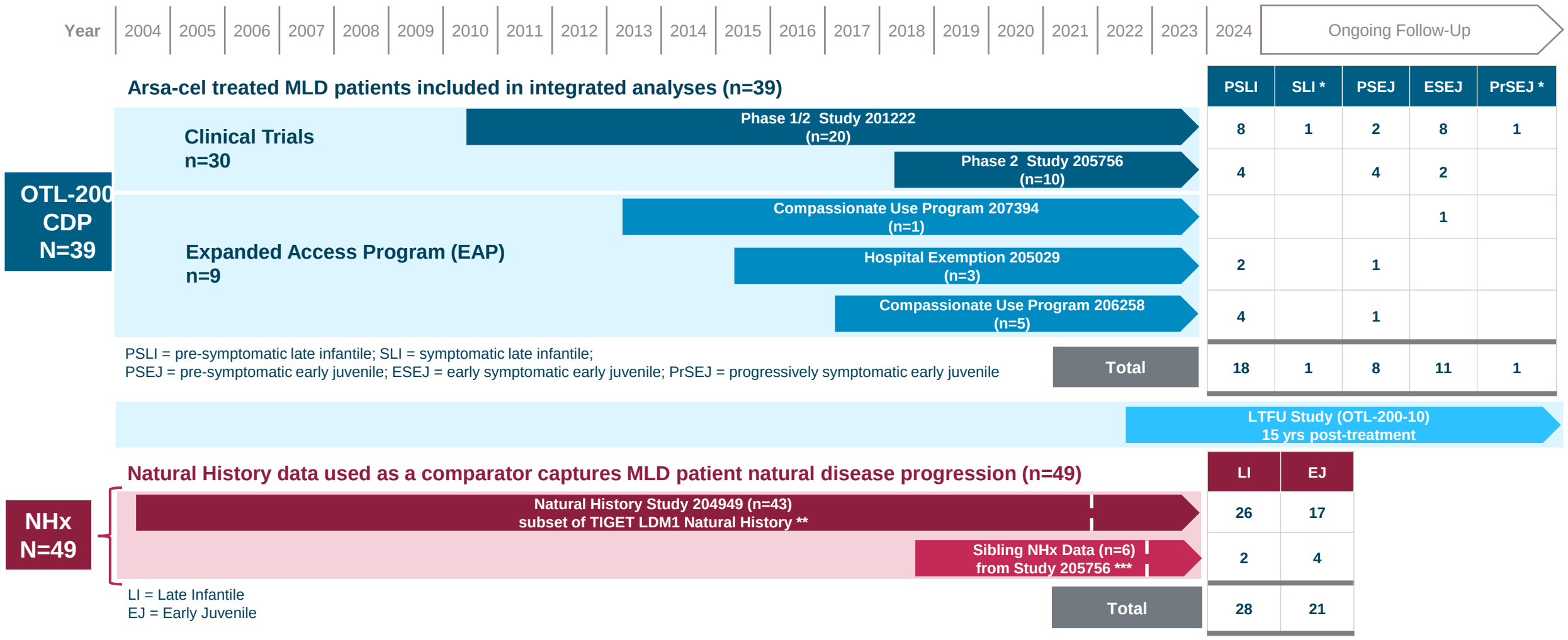
Integrated Analysis: Clinical Development Program (CDP)



PSLI	SLI *	PSEJ	ESEJ	PrSEJ *
8	1	2	8	1
4		4	2	
			1	
2		1		
4		1		
18	1	8	11	1

LI	EJ
26	17
2	4
28	21

* Two patients were treated under a previous version of the protocol for Study 201222 (NCT01560182) and would have been ineligible for treatment under subsequent protocol versions. These patients were treated while in the rapidly progressive phase of MLD and did not benefit from treatment, so efficacy analyses on these patients are not presented (safety data only)
** Natural history study started in 2004, but retrospective data were collected from year 2000 onwards
*** Data only included in analyses of severe motor impairment free survival and overall survival.

Calbi V, et al. Presented at: Society for the Study of Inborn Errors of Metabolism (SSIEM), 30 Aug 2023, Jerusalem, Israel

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Integrated Analysis: Clinical Eligibility

Inclusion Criteria [1-2]

- Pre-symptomatic late infantile (LI) patients
- Pre- or early-symptomatic early juvenile (EJ) patients

MLD diagnosis is based on ARSA enzyme activity detection in PB cells below the normal range and presence of biallelic pathogenic or likely pathogenic variants in the *ARSA* gene, corroborated by increased urine sulfatides

Exclusion Criteria [1-2]

- enrolled in other trials
- underwent allogeneic HSCT in previous 6 months
- underwent allogeneic HSCT with evidence of residual cells of donor origin
- end-organ functions or any other severe disease, in the judgement of the investigator, would make the patient inappropriate for entry into this study
- HIVRNA and/or HCVRNA and/or HBVDNA positive
- neoplastic disease
- cytogenetic alterations typical of MDS/AML

The enrollment criteria and study design for the expanded access programs (EAP) was similar to those for the registrational clinical trial

Variant	Age at onset of symptoms	Mutations	Instrumental signs of severity
Late Infantile	In older sibling(s): ≤30 months	Two null (0) mutant ARSA alleles	Peripheral neuropathy at ENG study
Early Juvenile	In patient or older sibling(s): 30 months to <7 years	One null (0) and 1 R mutant ARSA allele(s)	Peripheral neuropathy at ENG study

Patients must meet 2 of 3 of the criteria (age, mutation, signs) required

Status	Determination [1-2]
Pre-symptomatic	Absence of neurological impairment (disease-related symptoms), with or without signs of the disease revealed by instrumental evaluations (ENG and brain MRI)
Early-symptomatic	Intelligence Quotient (IQ) ≥85 and GMFC-MLD ≤1 (Before the disease enters its rapidly progressive phase)

Early-symptomatic definition per most recent trial design for study 205756 (NCT03392987) [2]

ARSA, arylsulfatase A; DNA, deoxyribonucleic acid; RNA, ribonucleic acid; HBV, hepatitis B virus ; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplant; ENG, electronystagmography; MDS/AML myelodysplastic syndromes / acute myeloid leukemia; MRI, magnetic resonance imaging.

1. https://clinicaltrials.gov/ct2/show/NCT01560182 Accessed April 26, 2019. 2. https://clinicaltrials.gov/ct2/show/NCT03392987 Accessed June 5, 2020.

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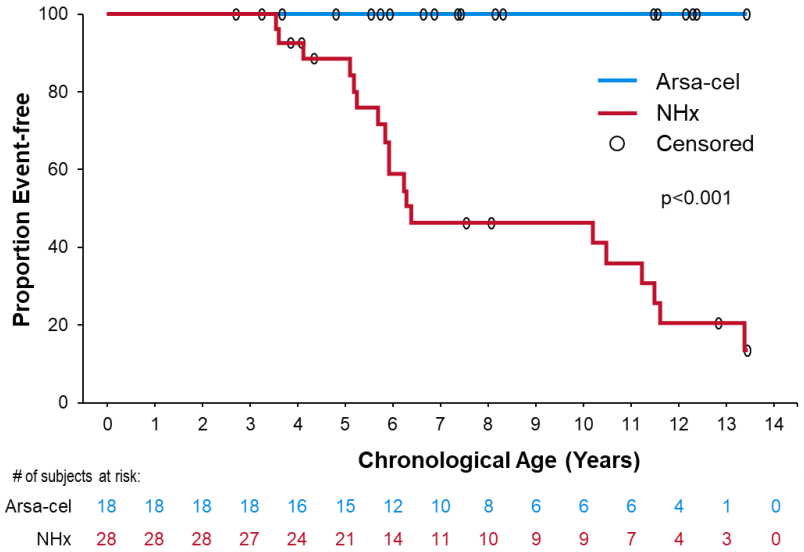
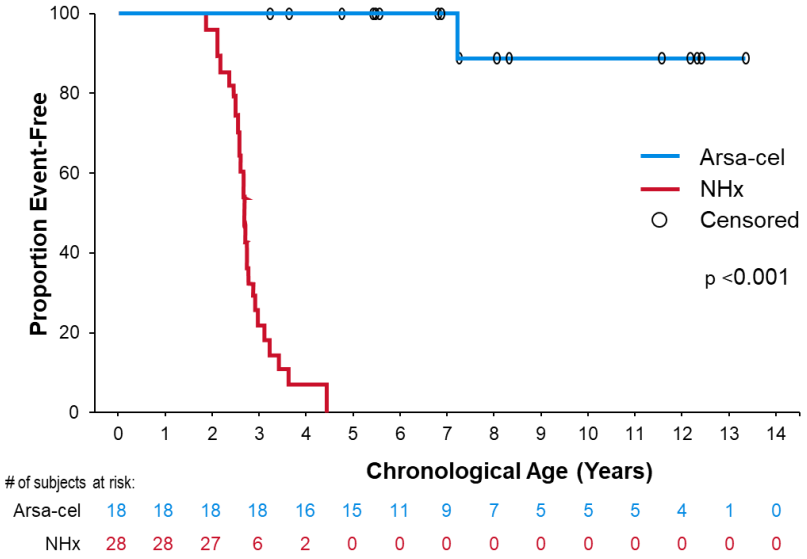
Integrated Analysis: Arsa-cel vs. NHx – Clinical Outcomes

Pre-Symptomatic Late Infantile (PSLI)

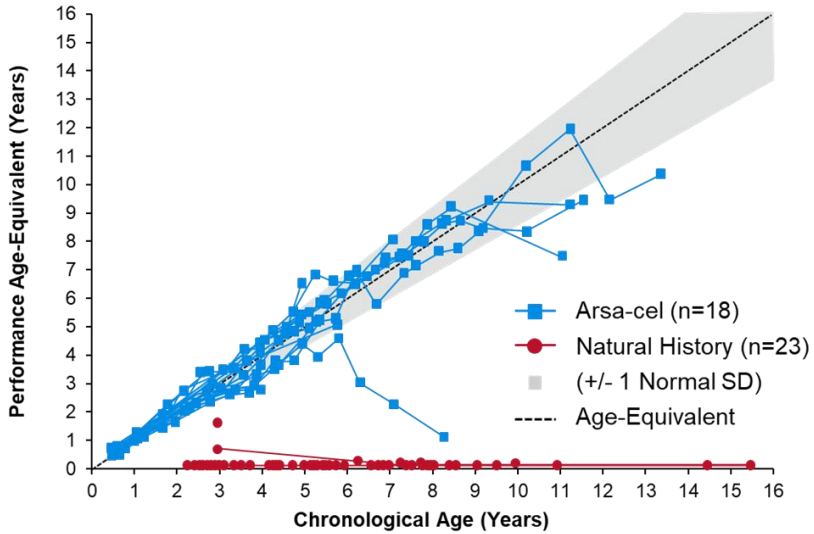
Overall Survival (OS)



Severe Motor Impairment Free Survival (sMFS)



Cognitive Performance Age Equivalent



Estimated Proportion Event-Free Up To 6 Years of Age*

	Overall Survival (OS) Interval from birth to death from any cause	Severe Motor Impairment Free Survival (sMFS) Interval from birth to first occurrence GMFC-MLD ≥ 5 (no locomotion and unable to sit) or death	Cognitive Performance Age Equivalent Estimate of the neurocognitive developmental age
Arsa-cel	100%	100%	Majority of patients acquire skills as expected for age **
NHx	59%	0%	None of the NHx patients acquired skills as expected for age

Arsa-cel treated PSLI patients exhibit a clinically meaningful improvement in OS, sMFS, and cognition as compared to LI NHx patients.
LI NHx patients experience rapid loss of motor function, severe cognitive impairment, and ultimately death.

If no event is recorded, subject is censored at the last GMFC assessment (SMFS; MFS) or the last contact date (OS).
* Estimated proportion event-free up to 6 years of age was selected as a clinically relevant timepoint for SMFS and OS as by this age all LI NHx patients have experienced severe motor impairment or death ** Cognitive performance age equivalent as of last follow-up.
GMFC-MLD, Gross Motor Function Classification-Metachromatic Leukodystrophy; NHx, natural history.
Fumagalli F. et al. Presented at: 20th Annual WORLD Symposium; February 7, 2024, San Diego, CA, USA.

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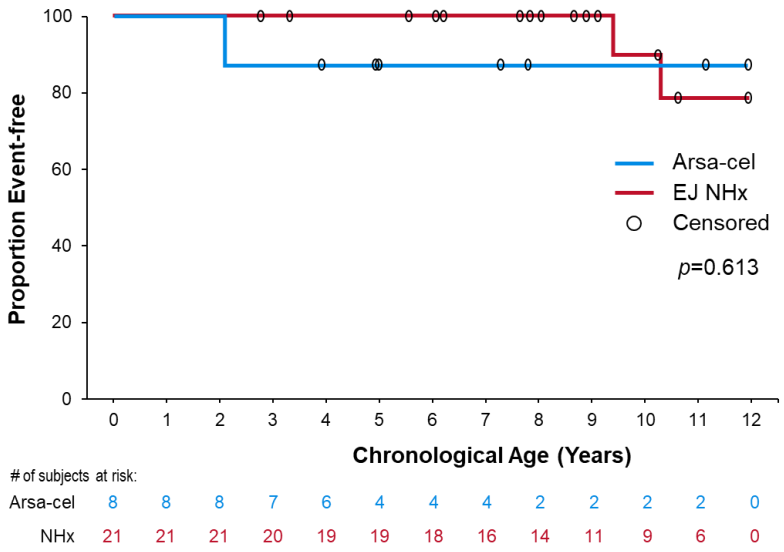
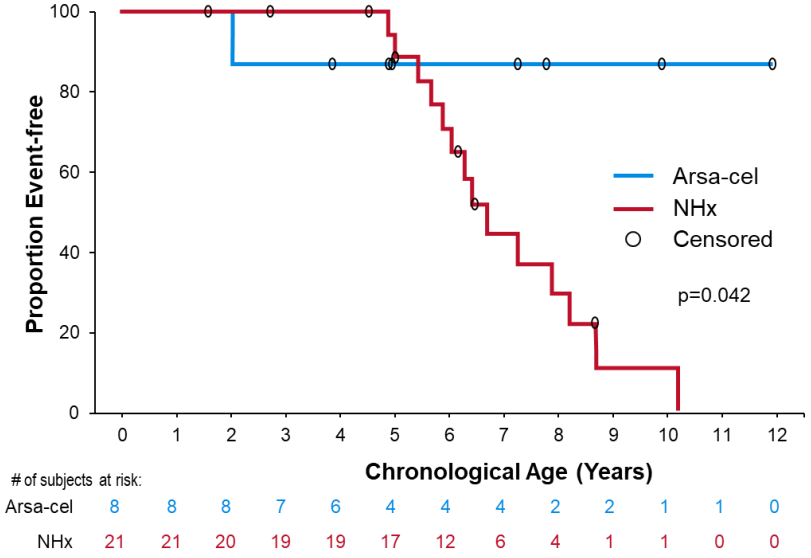
Integrated Analysis: Arsa-cel vs. NHx – Clinical Outcomes

Pre-Symptomatic Early Juvenile (PSEJ)

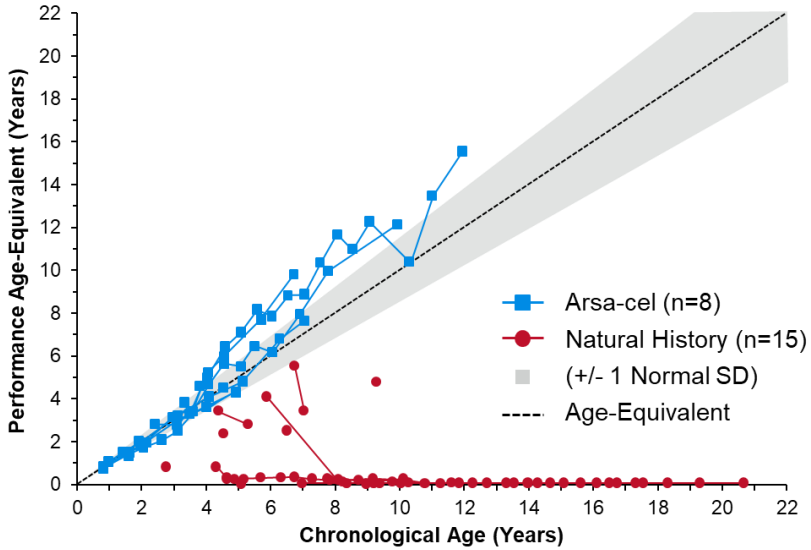
Overall Survival (OS)



Severe Motor Impairment Free Survival (sMFS)



Cognitive Performance Age Equivalent



Estimated Proportion Event-Free Up To 10 Years of Age*

	Overall Survival (OS) Interval from birth to death from any cause	Severe Motor Impairment Free Survival (sMFS) Interval from birth to first occurrence GMFC-MLD ≥ 5 (no locomotion and unable to sit) or death	Cognitive Performance Age Equivalent Estimate of the neurocognitive developmental age
Arsa-cel	87.5%	87.5%	All surviving patients acquire skills as expected for age**
NHx	90%	11.2%	None of the NHx patients acquired skills as expected for age

Arsa-cel treated PSEJ patients exhibit a clinically meaningful improvement in sMFS and preservation of cognition as compared to EJ NHx patients. EJ NHx patients experience loss of motor function and severe cognitive impairment; those that survive are in a severely debilitated state.

If no event is recorded, subject is censored at the last GMFC assessment (SMFS; MFS) or the last contact date (OS).
* Estimated proportion event-free up to 10 years of age was selected as a clinically relevant timepoint for SMFS as by this age almost all EJ NHx patients have experienced severe motor impairment ** Cognitive performance age equivalent as of last follow-up
GMFC-MLD, Gross Motor Function Classification-Metachromatic Leukodystrophy; NHx, natural history.
Fumagalli F. et al. Presented at: 20th Annual WORLD Symposium; February 7, 2024, San Diego, CA, USA.

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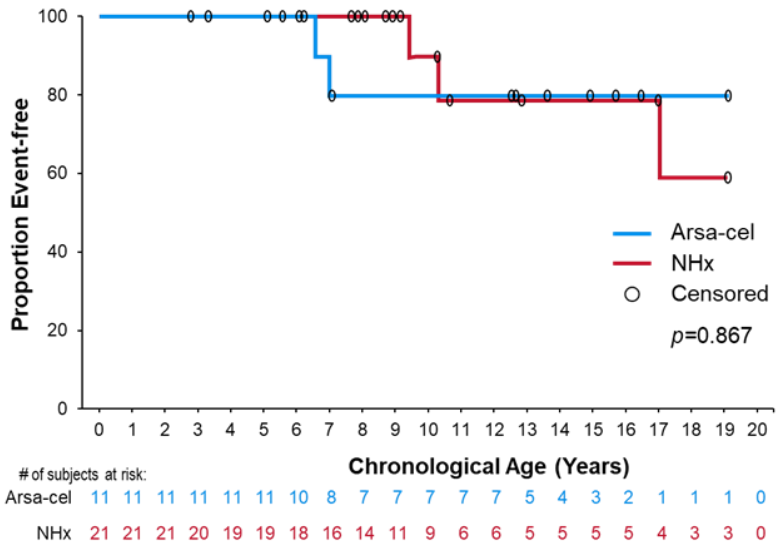
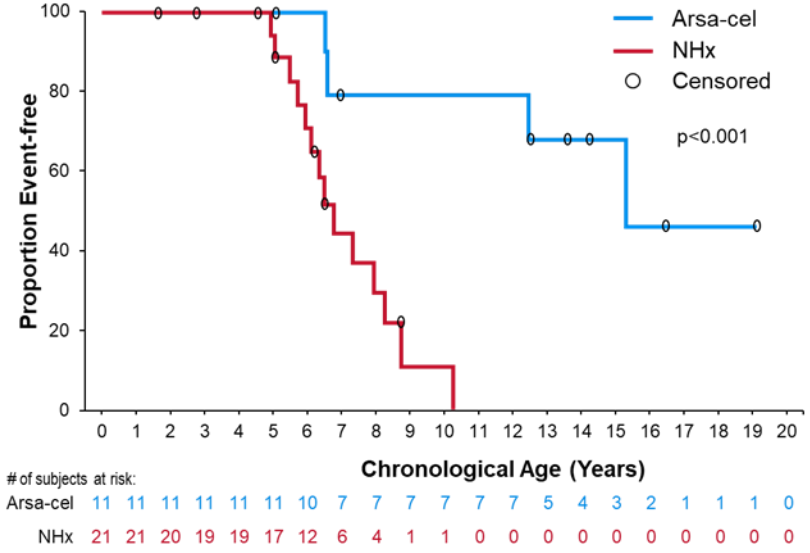
Integrated Analysis: Arsa-cel vs. NHx – Clinical Outcomes

Early-Symptomatic Early Juvenile (ESEJ)

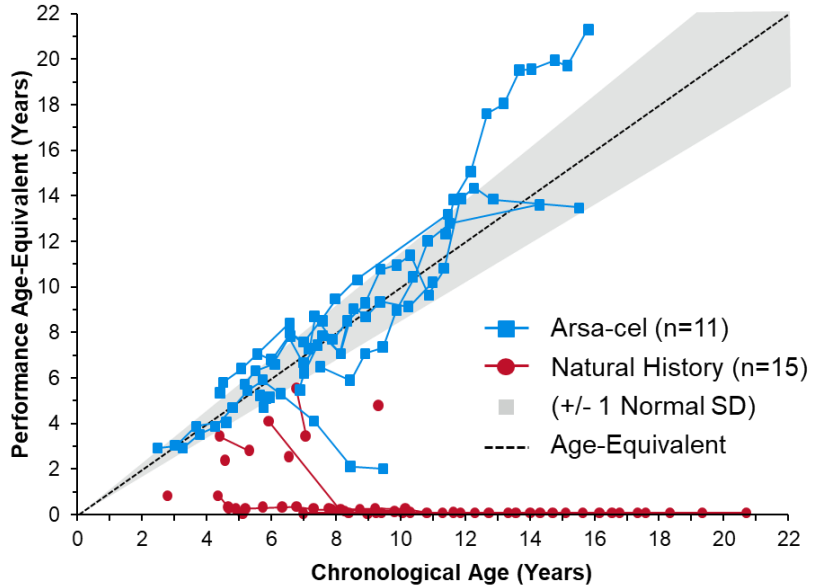
Overall Survival (OS)



Severe Motor Impairment Free Survival (sMFS)



Cognitive Performance Age Equivalent



Estimated Proportion Event-Free Up To 10 Years of Age*

	Overall Survival (OS) Interval from birth to death from any cause	Severe Motor Impairment Free Survival (sMFS) Interval from birth to first occurrence GMFC-MLD ≥ 5 (no locomotion and unable to sit) or death	Cognitive Performance Age Equivalent Estimate of the neurocognitive developmental age
Arsa-cel	80%	80%	Majority of surviving patients acquire skills as expected for age**
NHx	90%	11.2%	None of the NHx patients acquired skills as expected for age

Arsa-cel treated ESEJ patients exhibit a clinically meaningful improvement in sMFS and preservation of cognition as compared to EJ NHx patients. EJ NHx patients experience loss of motor function and severe cognitive impairment; those that survive are in a severely debilitated state.

If no event is recorded, subject is censored at the last GMFC assessment (SMFS; MFS) or the last contact date (OS).
* Estimated proportion event-free up to 10 years of age was selected as a clinically relevant timepoint for SMFS as by this age almost all EJ NHx patients have experienced severe motor impairment ** Cognitive performance age equivalent as of last follow-up
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Fumagalli F. et al. Presented at: 20th Annual WORLD Symposium; February 7, 2024, San Diego, CA, USA.

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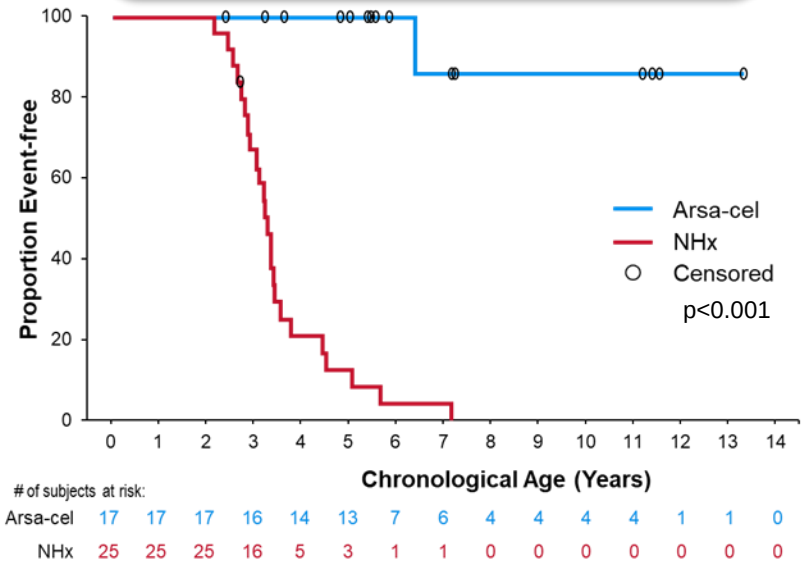
Arsa-cel vs. NHx: Age at Loss of Speech

Age at Loss of Speech

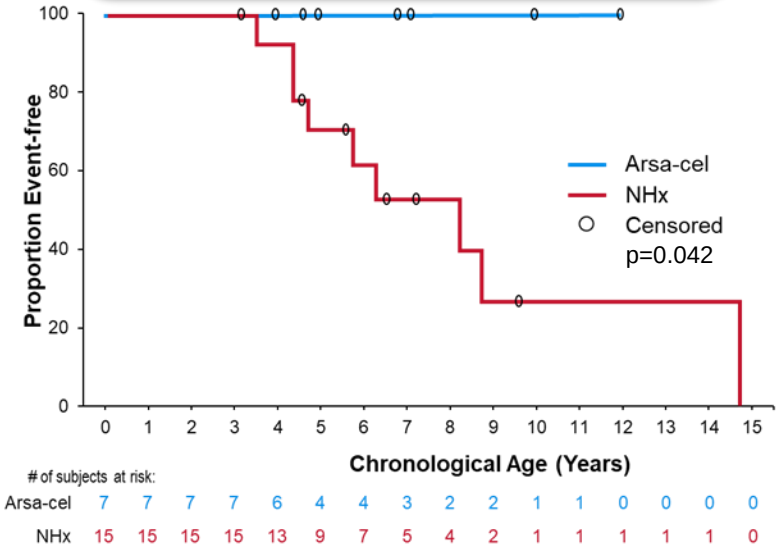
Interval from birth to loss of speech (first record of 'incomprehensible sounds/muteness') or death due to disease progression

PSLI



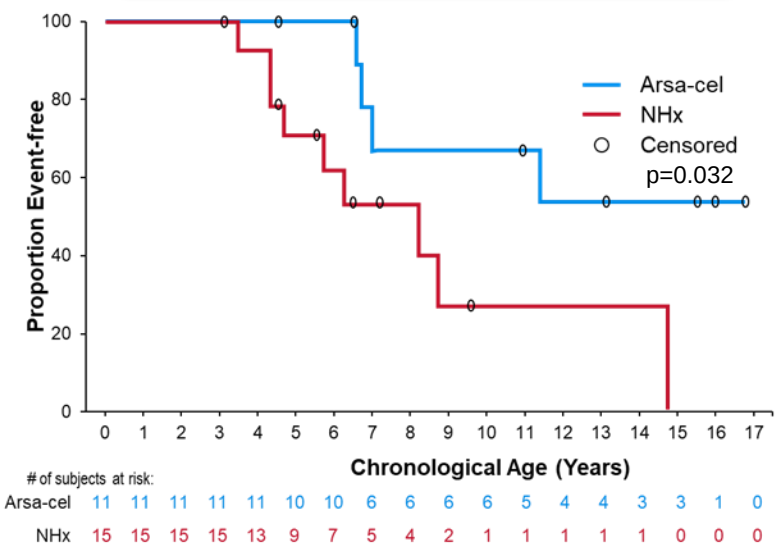
Estimated proportion event-free up to 6 years of age	
Arsa-cel	LI NHx
100%	4.2%

PSEJ



Estimated proportion event-free up to 10 years of age	
PSEJ: Arsa-cel	EJ NHx
100%	26.5%

ESEJ



Estimated proportion event-free up to 10 years of age	
ESEJ: Arsa-cel	EJ NHx
66.7%	26.5%

Arsa-cel preserved speech in all treated subgroups as compared to NHx
Most NHx patients experienced loss of speech

If no event is recorded, subject is censored at the last assessment or the last contact date

Calbi V, et al. Presented at: Society for the Study of Inborn Errors of Metabolism (SSIEM), 30 Aug 2023, Jerusalem, Israel

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Integrated Analysis: Safety Summary

Median follow up: 6.76 years (range: 0.64 to 12.19); N=39
Total patient-years follow-up = 251.23

With continued long-term follow-up, arsa-cel remains generally well tolerated.
No deaths or SAEs related to arsa-cel.

Potential Relation to:	Event	Description
Busulfan Conditioning	AEs	• Febrile neutropenia (32/39), stomatitis (29/39), VOD (2/39). (Grade ≥ 3 events)
	SAEs	• Vomiting (1/39), VOD (1/39), Anemia (1/39),Thrombocytopenia (1/39) Sepsis (1/39) (Grade 3 events) • Delayed platelet engraftment (4/39) (resolved within the first 4 months after conditioning. No bleeding events reported) • Patient who despite engraftment, experienced prolonged anemia and thrombocytopenia (required infusion of unmanipulated back-up cells)
Arsa-cel	AEs	• N = 6 events of transient anti-ARSA antibodies (5 of 6 events resolved spontaneously or after short course of rituximab, 1 event ongoing at time of data-cut-off. No impact on clinical outcomes)
	SAEs	• No treatment related SAEs (Polyclonal reconstitution with no evidence of clonal expansion, malignancy, or replication competent lentivirus)

N = 3 Deaths, 1 patient due to ischemic cerebral infarction (PSEJ) not related to treatment and 2 patients due to rapid disease progression (at 8- and 15-months post-treatment (both ESEJ)

Adverse Events (AEs), Serious Adverse Events (SAEs), veno-occlusive disease (VOD)
* AEs and SAEs associated with MLD Disease Progression not included in Safety Summary

 Calbi V, et al. Presented at: Society for the Study of Inborn Errors of Metabolism (SSIEM), 30 Aug 2023, Jerusalem, Israel

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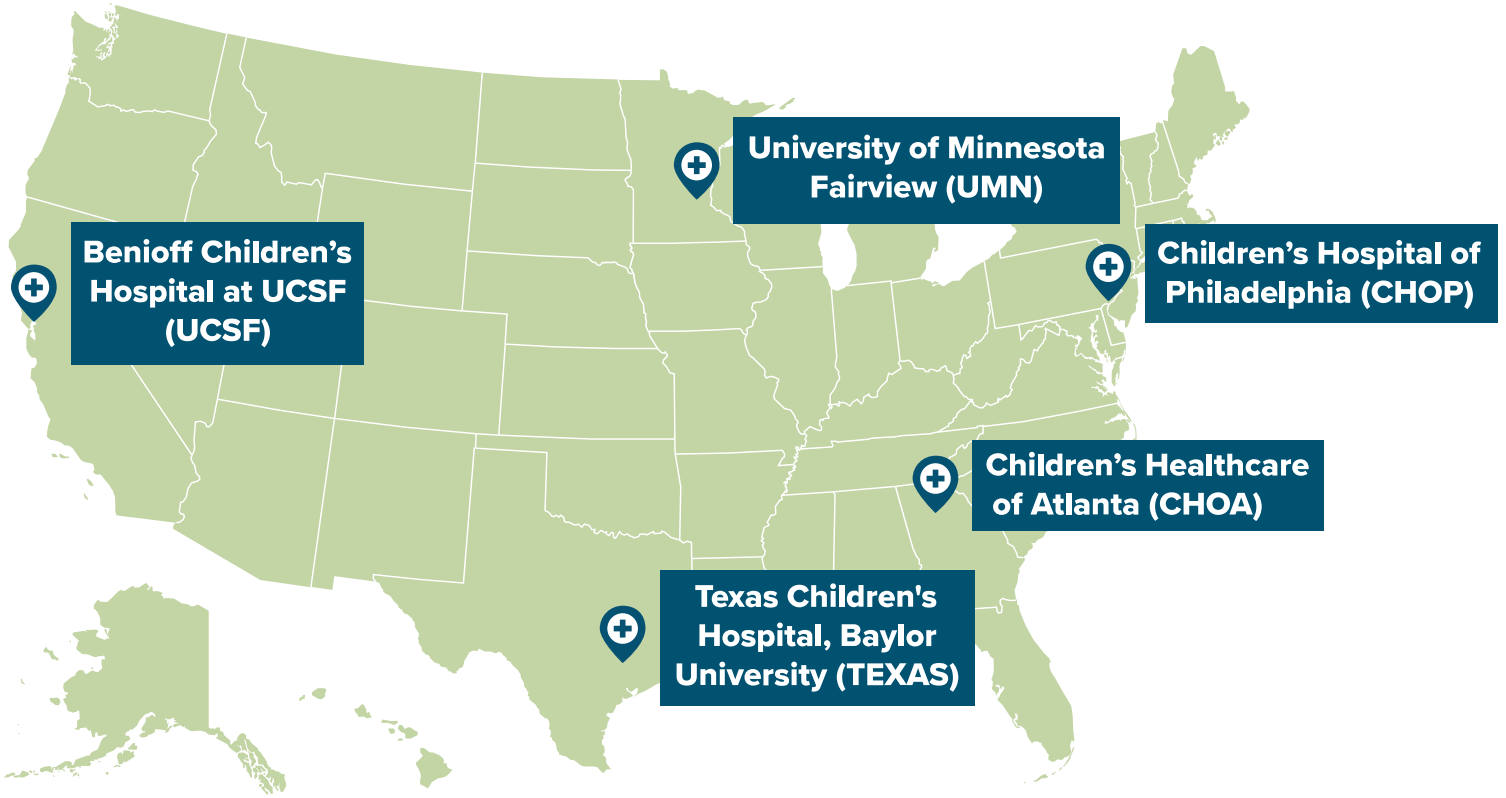
Arsa-cel will be offered at a select network of Qualified Treatment Centers (QTCs)*



- The QTC network has been carefully selected and trained to administer arsa-cel
- Considerations for QTC participation included:
  - Clinical expertise
  - Geographic considerations
  - Limited sites at launch
  - Distribution and logistics
  - Access and reimbursement
  - Contracting

*Some treatment centers are currently awaiting final confirmation.

QTCs are independently owned and operated. Orchard Therapeutics does not have oversight over any QTC or the medical care they provide. Contact the QTC or Orchard Assist for additional information. Inclusion of a QTC on this map does not represent an endorsement, referral, or recommendation from Orchard Therapeutics. It is the sole discretion of patients and their healthcare professional to determine which QTC may be the best fit for them. Please note that the circumstances of coverage may vary based on the QTC. An Orchard Assist representative may be able to provide information about insurance coverage.

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Expert consensus guidelines strongly recommend treatment with arsa-cel as the standard of care for early-onset MLD[1,2]

Cytotherapy 000 (2024) 1–10

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Consensus guidelines for the monitoring and management of metachromatic leukodystrophy in the United States

Laura A. Adang[1,20,*], Joshua L. Bonkowsky[2], Jaap Jan Boelens[3], Eric Mallack[4], Rebecca Ahrens-Nicklas[1], John A. Bernat[5], Annette Bley[6], Barbara Burton[7], Alejandra Darling[8], Florian Eichler[9], Erik Eklund[10], Lisa Emrick[11], Maria Escolar[12,13], Ali Fatemi[4], Jamie L. Fraser[14], Amy Gaviglio[15,30], Stephanie Keller[16], Marc C. Patterson[17,18,31], Paul Orchard[19], Jennifer Orthmann-Murphy[20], Jonathan D. Santoro[21], Ludger Schöls[22], Caroline Sevin[23], Isha N. Srivastava[24], Deepa Rajan[25], Jennifer P. Rubin[7], Keith Van Haren[24], Melissa Wasserstein[26], Ayelet Zerem[27], Francesca Fumagalli[28], Lucia Laugwitz[29], Adeline Vanderver[1,20]

European Journal of Paediatric Neurology 49 (2024) 141–154

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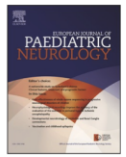

Original article

Newborn screening in metachromatic leukodystrophy – European consensus-based recommendations on clinical management

Lucia Laugwitz[a,b,*,1], Daphne H. Schoenmakers[c,d,e,1], Laura A. Adang[f], Stefanie Beck-Woedl[b], Caroline Bergner[g], Geneviève Bernard[h,i,j], Annette Bley[k], Audrey Boyer[l], Valeria Calbi[m,q], Hanka Dekker[n], Florian Eichler[o], Erik Eklund[p], Francesca Fumagalli[m,q,r], Francesco Gavazzi[s], Sabine W. Grønborg[t], Peter van Hasselt[u], Mirjam Langeveld[v], Caroline Lindemans[w], Fanny Mochel[x], Andreas Oberg[y], Dipak Ram[z], Elise Saunier-Vivar[l], Ludger Schöls[aa], Michael Scholz[ab], Caroline Sevin[ac], Ayelet Zerem[ad], Nicole I. Wolf[c,d,2], Samuel Groeschel[a,2]

Key recommendations

It is **strongly recommended** to initiate treatment in identified individuals before symptom onset

It is **strongly advised** to treat any early onset presymptomatic individual with arsa-cel who has been identified by NBS

It is **suggested** to treat late onset MLD (LJ and adult onset) with allo-HSCT

For **unclear disease onset**, systemic monitoring is crucial to enable early treatment during subclinical disease stages

1. Laugwitz L et al Eur J Paediatr Neurol. 2024;49:141-154. 2. Adang LA et al. Cytotherapy. 2024;26(7):739-748.

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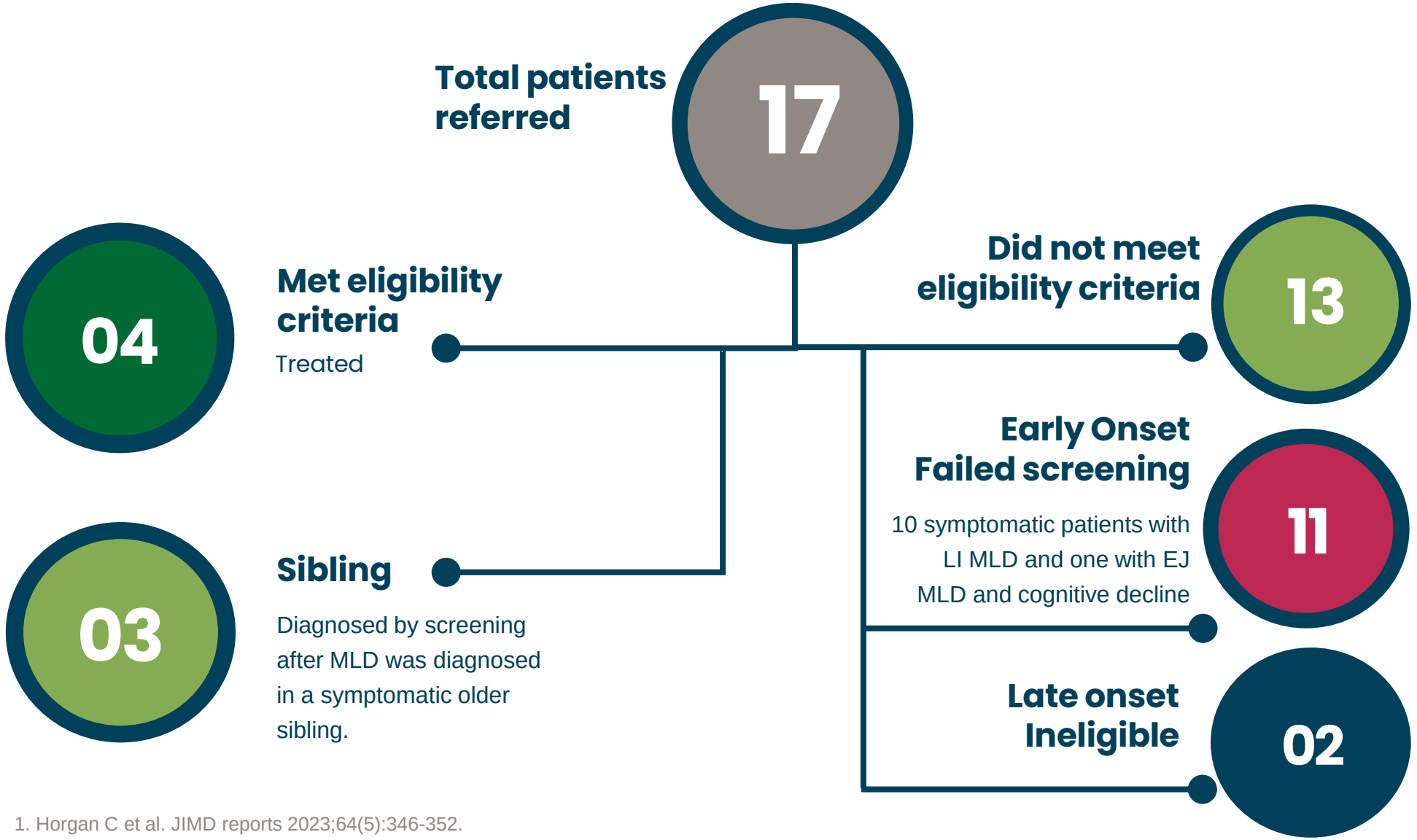
Impact of Newborn Screening

Without newborn screening, majority of patients referred for treatment are ineligible for arsa-cel therapy (Horgan et al., 2023)[1]



1. Horgan C et al. JIMD reports 2023;64(5):346-352.

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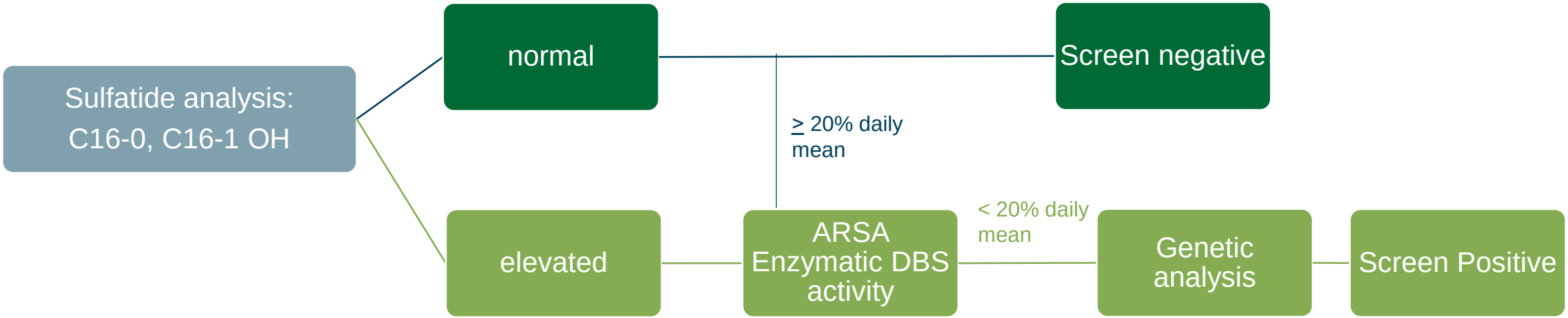
Newborn Screening Approach for MLD

Global adoption of MLD NBS algorithm[1-3]



A two-tiered approach for NBS starting with LC-MS/MS analysis with an optional third molecular sequencing tier is recommended as follows:

1st tier = C16:0 sulfatide and C16:1-OH sulfatide in dried blood spots (DBS) using liquid chromatography-tandem mass spectrometry (LC-MS/MS).

2nd tier = ARSA enzyme activity in DBS using LC-MS/MS.

3rd tier = *ARSA* gene sequencing (feasible in DBS).

MLD internal standards, calibrators and controls available for sulfatide and ARSA enzyme DBS assays

1. Hong X et al. Genet Med. 2021;23(3):555–561. 2. Bekri S et al. Mol Genet Metab. 2024; 142(1):108436
3. Laugwitz L et al. N Engl J Med. 2024 Sep 18. Epub ahead of print.

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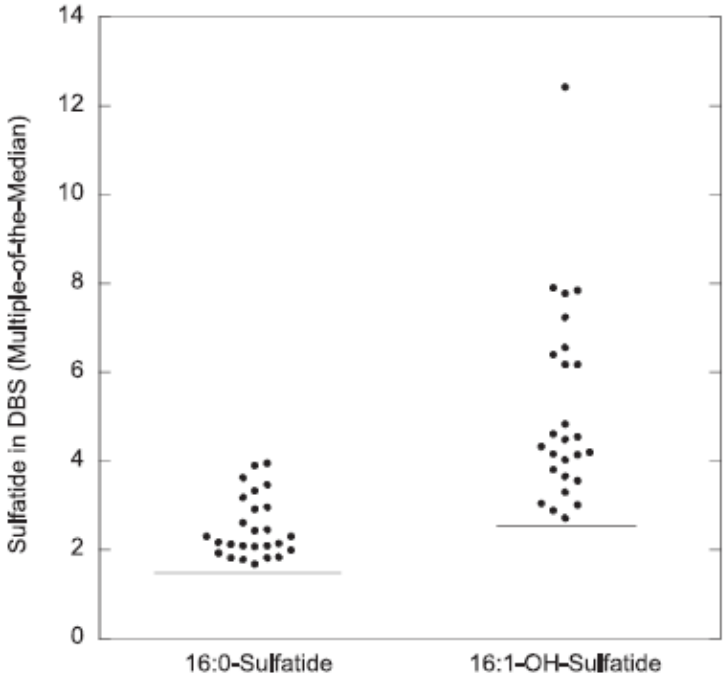
High precision first tier test for MLD minimises false positives & screens out pseudodeficiencies[1, 2]

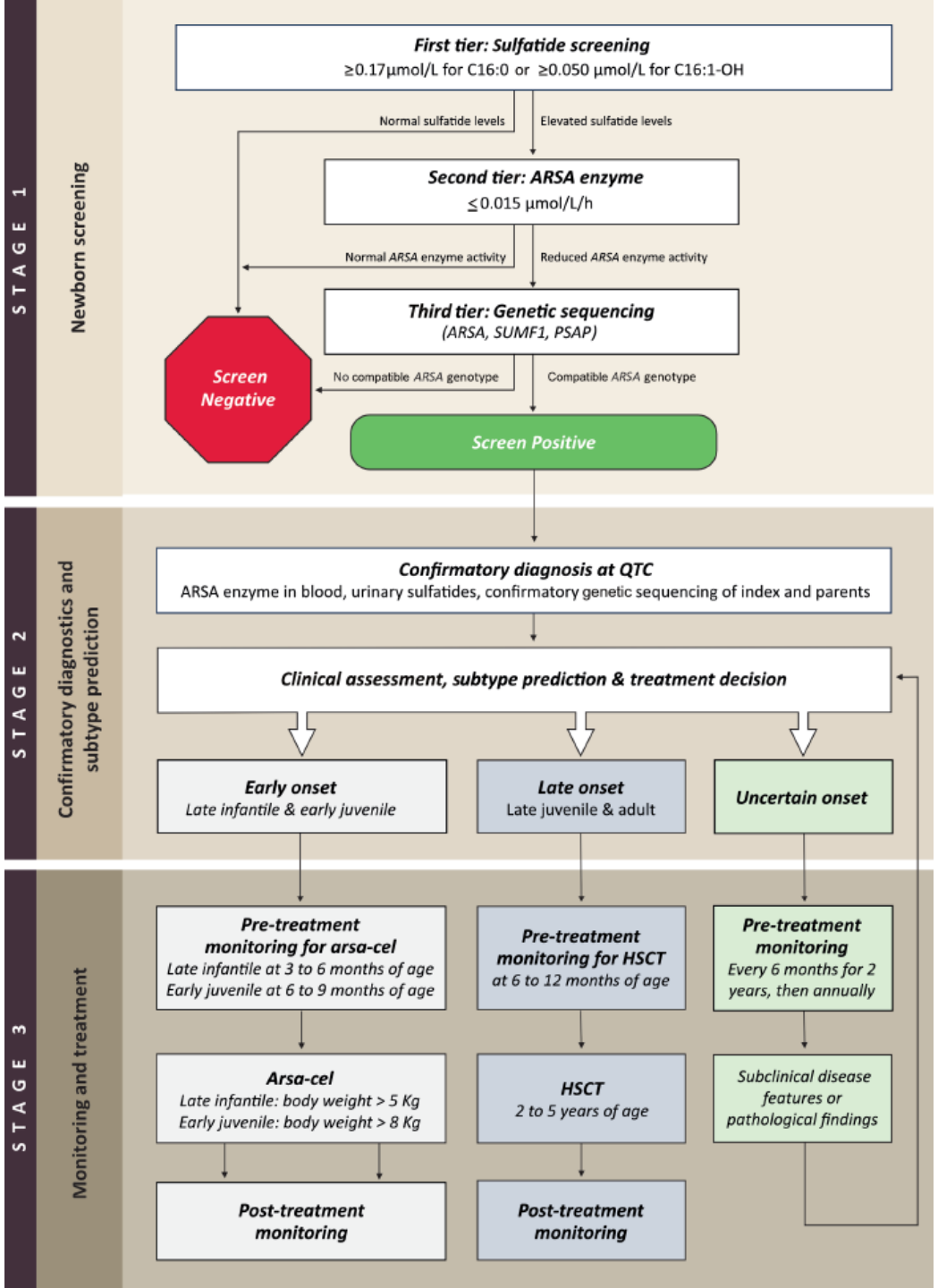


MoM values for C16:0 and C16:1-OH for 40 clinically confirmed MLD newborns

C16:0 and C:16:1-OH serve as the best first tier screening sulfatides for MLD with a false positive rate of essentially zero (0.048%)

1. Bekri S et al. Mol Genet Metab. 2024; 142(1):108436 2. Laugwitz L et al. N Engl J Med. 2024 Sep 18. Epub ahead of print.

Screening and care pathway available for all cases of MLD identified on newborn screening[1]



1. Laugwitz L et al. N Engl J Med. 2024 Sep 18. Epub ahead of print.

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Global Newborn Screening Experience

- Retrospective analysis of 27,000 dried blood spots in Washington revealed 1 MLD patient (Hong et al., 2021)[1]
  - In 2020, of 27,335 dried blood spots screened for C16:0 sulfatide species, 195 moved to ARSA enzyme assay, 2 had abnormal ARSA enzyme, 1 MLD patient identified
- Retrospective analysis of 3,687 de-identified dried blood spots analyzed in pre-pilot newborn screening feasibility study in Manchester, UK (Wu et al., 2024)[2]
  - Through further refining cut-off for C16:0 sulfatide, 1 late infantile MLD patient was incidentally identified leading to urgent ethics review, identification of blood spot, referral to LSD specialist, and initiation of arsa-cel treatment
- Newborn Screening and Presymptomatic Treatment of Metachromatic Leukodystrophy; Prospective study (Laugwitz et al.,2024)[3]
  - Starting in 2021, 109,259 babies screened via C16:0 and C16:1-OH sulfatide species, 381 cases moved to ARSA enzyme assay and concurrent genetic testing, 3 MLD patients identified
    - 2 patients with early juvenile → initiated arsa-cel
    - 1 patient with late-onset, initiated serial screening to plan for allo-HSCT
    - No false positives identified
- Ongoing efforts:
  - Implementation of MLD NBS ongoing in Norway and Illinois
  - Prospective pilot at Rouen University Hospital in Rouen, France; Prospective pilot at Meyer's Children's Hospital in Florence, Italy; Prospective pilot study at King Fahad Medical Center in Saudi Arabia

1. Hong X et al. Genet Med. 2021;23(3):555–561. 2. Wu THY et al. Mol Genet Metab. 2024;142(1):108349
3. Laugwitz L et al. N Engl J Med. 2024 Sep 18. Epub ahead of print.

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Newborn Screening Experience: ScreenPlus[1]

- Ongoing prospective pilot study of 14 disorders utilizing an analyte based, multi-tiered screening platform to evaluate and enhance screening accuracy

- 14 disorders selected for inclusion in the initial panel: Acid Sphingomyelinase Deficiency (ASMD, or Niemann-Pick type A and B), Ceroid Lipofuscinosis type 2 (CLN2), Cerebrotendinous Xanthomatosis (CTX), Fabry Disease, GM1 gangliosidosis, Gaucher Disease, Lysosomal Acid Lipase deficiency (LAL—D), Metachromatic Leukodystrophy (MLD), Mucopolysaccharidosis (MPS) II (Hunter Syndrome), MPS IIIb (Sanfilippo type 3b), MPS IVa (Morquio syndrome), MPS VI (Maroteaux-Lamy syndrome), MPS VII (Sly Syndrome), Niemann-Pick Disease Type C (NPC)

- Disorders chosen based on
  - 1. A dried blood spot (DBS) assay that can be multiplexed and that is high-throughput, reasonably priced, and has had positive baseline validation studies
  - 2. Significant morbidity or mortality if untreated
  - 3. A pediatric phenotype
  - 4. An FDA-approved treatment(s) or treatment(s) currently in a clinical trial

1. Kelly NR et al. Mol Genet Metab Rep. 2023 Dec 14;38:101037.

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On June 27th, a nomination was made to the ACHDNC to include MLD on the RUSP

On August 9th, the ACHDNC unanimously voted to move the RUSP nomination for metachromatic leukodystrophy to the evidence review phase making MLD the *fastest* disorder to move from nomination to evidence review by the ACHDNC.

1. Human Resources & Service Administration. Summary of Nominated Conditions to the Recommended Uniform Screening Panel (RUSP), Aug 2024.

The MLD NBS Alliance is a community of experts dedicated to contributing knowledge and expertise to establish newborn screening for MLD.

2nd Annual US MLD NBS Alliance Meeting will be in Minnesota in April 2025