ACHDNC
Advisory Committee on Heritable Disorders in Newborns and Children

Nomination and Prioritization Workgroup Report on:
Metachromatic Leukodystrophy (MLD)

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ACHDNC Nomination and Prioritization Workgroup:

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Nomination of Metachromatic Leukodystrophy (MLD)

Nominators

MLD Foundation

*MLD RUSP Submission Workgroup Members:

Name	Professional Affiliation (if any)
Laura Adang, MD, PhD, MSTR	MLD clinical researcher at the Children's Hospital of Philadelphia
Lesa Brackbill, MA	Leukodystrophy Newborn Screening Network
Barbara Burton, MD	MLD clinician and clinical researcher at the Northwestern University, Feinberg School of Medicine
Diane Fennimore, MBA	United Leukodystrophy Foundation
Michael Gelb, PhD	Biochemical researcher and newborn screening expert at the University of Washington in Seattle
Maria Kefalas, PhD	Calliope Joy Foundation/Cure MLD
Joan Keutzer, PhD	Newborn screening and rare diseases expert
Paul Orchard, MD	MLD gene therapy/transplant expert and clinical researcher at the University of Minnesota Medical School
Joe Orsini, PhD	Deputy Director, New York State Newborn Screening Program
Marc Patterson, MD	MLD and rare diseases clinical researcher at the Mayo Clinic
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Nominated Condition

- Early Onset (both types) Metachromatic Leukodystrophy (MLD)

MLD Condition Information

- MLD is:
- Autosomal recessive
- Life-shortening
- Caused by dysfunctional Arylsulfatase A enzyme (ARSA) leading to a build-up of sulfatides
- Sulfatide build-up affects central and peripheral nervous systems and invokes an inflammatory response

MLD Clinical Presentation

Clinical Presentation (1/40K – 1/100K):

- Early Onset – Late Infantile (LI): motor delays followed by predictable decline and death in early childhood;
- Early onset – Early Juvenile (EJ): behavioral and cognitive changes followed by loss of motor function; death in adolescence
- Late onset neuropsychiatric symptoms; variable

MLD Treatment and Management

- Management:
- **Early onset:** Late Infantile (LI) and Early Juvenile (EJ)
  - Onset 30 months to 7 years treated before symptoms with Lenmeldy (gene therapy with CD34+ cells transduced with a lentiviral vector containing human *ARSA*; 8 kg requirement); **target of screening**
- **Late onset:** Late juvenile (LJ) and adult
  - Onset 7 years to adulthood; monitoring and treated with hematopoietic stem cell transplantation

Core Requirements for Nomination

1. Validity of the laboratory test
2. Widely available confirmatory testing with a sensitive and specific diagnostic test
3. A prospective population-based pilot study

Key Questions to Address

1. Is the nominated condition(s) medically serious?
2. Is the case definition and the spectrum of the condition(s) well-described to help predict the phenotypic range of those children who will be identified based on population-based screening?
3. Are prospective pilot data from population-based assessments available for this condition?
4. Does the screening test(s) have established analytic validity?
5. Are the characteristic of the screening test(s) reasonable for the newborn screening system (among other aspects, a low rate of false positives)?
6. Is there a widely available confirmatory test or diagnostic process, with CLIA and/or FDA approval?
7. Are there defined treatment protocols for the condition when identified pre-symptomatically and treatment is generally available?
8. Do the results have clinical utility balancing benefits and harms?
9. Will screening identify those most likely to benefit from treatment?

Key Question 1: Is the nominated condition(s) medically serious?

Yes

Clinical Presentation (1/40K – 1/100K):

- Early Onset – Late Infantile (LI): motor delays followed by predictable decline and death in early childhood;
- Early Onset – Early Juvenile (EJ): behavioral and cognitive changes followed by loss of motor function; death in adolescence
- Late onset neuropsychiatric symptoms; variable

Key Question 2: Is the case definition and the spectrum of this condition well described, to help predict the phenotypic range of those children who will be identified based on population-based screening?

Yes

Overall Phenotype	Subtype	Symptom Onset	Percentage of Cases
Early-Onset	Late infantile (LI)	≤ 30 months	50-60%
	Early Juvenile (EJ)	30 months and 7 years	20-40%[a]
Late-Onset	Late Juvenile (LJ)	7 years and 16 years	
	Adult	≥ 17 years	10-20%

- Genotype – phenotype correlations are strong, but not definitive (~1,400 variants in ClinVar); null variants thought to be more severe; some 'common variants' align with phenotype
- Newborn screening will detect late-onset patients; target is pre-symptomatic early onset

Key Question 3: Are prospective pilot data (U.S. and/or international) from population-based assessments available for this condition?

Yes

- Hannover Germany screened 109,259 babies (C16:0, C16:0-OH, C16:1-OH)
- 381 screen positive (1 in 287) on 1st tier; changed parameters over time
- 230 available for enzyme analysis
- 20 with low enzyme results, subjected to DNA sequence analysis
- 3/20 had 2 *ARSA* variants (MLD diagnosis) and 3/20 *ARSA* carriers identified
- 2 of 3 cases early onset and 1 of 3 late onset
- Later sequenced all 381 and found 3 *ARSA* carriers; 3 *SUMF1* carriers and 4 *PSAP* carriers in addition to above. Three additional ARSA carriers were screen positive
- ****Screening will identify both types; acceptable monitoring protocol needed**

Key Question 3: Are prospective pilot data (U.S. and/or international) from population-based assessments available for this condition?

Yes

- Washington retrospective validation study tested 27,335 dried blood spots (Hong et al., 2023, rev. Bekri, 2024). In this study, 1 in 140 screened positive using first-tier C16:0 and required ARSA enzyme analysis.
- One "case" of MLD detected; noted 2 known variants detected; not clinically confirmed
- Retrospective study of known MLD specimens (40/40)
- Tested a replicate set of 592 specimens along with other global NBS programs using the C16:1-OH and 0/592 screened positive.
- Other pilot studies ongoing around the world; cases have been identified globally by newborn screening of "high-risk" populations.

Key Question 3: Are prospective pilot data (U.S. and/or international) from population-based assessments available for this condition?

Yes

New York ScreenPlus

- Enrolled 18,352 infants; 106 infants had C16:0 ≥ 0.25 mmol/L and specimens were subjected to DNA analysis *in lieu* of ARSA enzyme assay (not yet available in our laboratory)

- One in 173 screen positive (1st tier), 1 referral was false positive

Key Question 4: Does the screening test(s) have established analytic validity?

Conditional Yes

- Hannover study; accredited by ARCHIMEDlife Medical Laboratories using EN ISO 15189 in Austria
- Used 500 random DBS samples and 5 known MLD case NBS cards. The validation included carryover, cross-contamination, linearity, limit of detection, lower limit of quantification, intra-run precision, inter-run precision, and post processing stability.
- Proficiency testing via specimen exchange with Manchester group
- University of Washington (Bekri) and international collaboration using C16:1-OH

Key Question 5: Are the characteristics of the screening test(s) reasonable for the newborn screening system (among other aspects, a low rate of false positives)?

Yes

Three tier screen

- MLD sulfatide screening including C16:1-OH using LC/MS-MS
- ARSA enzyme analysis requires a silica gel clean-up step and a separate method on the MS/MS (LC-MS/MS).
- DNA sequence analysis of the ARSA gene. Expected to be low volume based on published work.

Key Question 5: Are the characteristics of the screening test(s) reasonable for the newborn screening system (among other aspects, a low rate of false positives)?

Yes

- MLD sulfatide screening can be multiplexed with Niemann-Pick disease, Pompe disease*, Krabbe disease*, Gaucher disease, Fabry disease, MPS I*, MPS II*, other MPS disorders, Tyrosinemia type I*, Adrenoleukodystrophy*, cerebrotendinous xanthomatosis and Niemann-Pick type C using LC-MS/MS;
- Programs leaning towards higher tier testing to improve specificity Centers for Excellence (Laugwitz, 2024)
- ARSA enzyme activity can be done internally / externally
- Sequencing can be done internally/externally
- Not time critical
- Expect 30-50 cases per year across the country; screening will identify a spectrum of cases, not atypical for screening

*already on RUSP

Key Question 6: Is there a widely available confirmatory test or diagnostic process, with CLIA- and/or FDA-approval as appropriate?

Yes

- There are CLIA approved laboratories to perform the confirmatory testing for *ARSA* enzyme analysis, urine sulfatide concentration and DNA sequence analysis, if not available as part of the newborn screen.
- Number of babies who will need confirmatory testing thought to be low
- No FDA-approved confirmatory test, but rare disease testing typically, at least currently is not FDA approved

Key Question 7: Are there defined treatment protocols for the condition when identified pre-symptomatically and treatment is generally available?

Yes

- Expert consensus and Delphi analysis on management of MLD (Adang, 2024 and Laugwitz, 2024)
- Lenmeldy package insert for administration of treatment
- National Qualified Treatment Centers**: M Health Fairview Masonic Children's Hospital, Minneapolis, Minnesota, Children's Healthcare of Atlanta, Georgia, Children's' Hospital of Philadelphia, Pennsylvania, Texas Children's Hospital, Houston, Texas and UCSF Benioff Children's Hospital, San Francisco, California

***Need to consider that detection of MLD through NBS will make all patients eligible for disease-modifying treatment, however with insurance and travel considerations, treatment may not be universally available.*

Key Question 8: Do the results have clinical utility, balancing benefits and harms?

Yes

- Retrospective survey in the UK showed after approval of gene therapy, 17 case records studied, only 4 would have been eligible at diagnosis because of either a previously affected sibling (n=3) and 1 identified early (asymptomatic at diagnosis); others had more advanced disease.
- NBS pilots use a natural history comparator
- Therapy has side effects commonly seen due to chemotherapy, complications with ARSA antibodies.
- Fumagalli et al., (2022): 29 treated patients either asymptomatic or early symptoms (IQ $\geq$70; walk 10 steps), 2 died due to disease progression (were symptomatic at treatment), 1 due to ischemic stroke after infection. Remainder alive with generally preserved cognition and motor function. Compared to a natural history cohort (n=31), who suffered from typical decline in the same timeframes

Key Question 9: Does screening identify those most likely to benefit from treatment?

Yes

- Screening will identify infants with MLD (early and late onset); early identification and treatment will prevent development of symptoms whether treatment is gene therapy or management and stem cell transplantation.
- To an extent genotype can predict early v. late onset
- Improved outcomes have been reported in the literature as described herein

Key Questions - Summary

YES	1. Is the nominated condition(s) ***medically serious***?
YES	2. Is the ***case definition*** and the spectrum of the condition(s) well described, to help predict the phenotypic range of those children who will be identified based on population-based screening.
YES	3. Are ***prospective pilot data*** from population-based assessments available for this condition?
YES/NO	4. Does the screening test(s) have established ***analytic validity***?
YES	5. Are the ***characteristics of the screening test(s)*** reasonable for the newborn screening system (among other aspects, a low rate of false positives)?
YES	6. Is there a widely available ***confirmatory test/diagnostic*** process, with CLIA and/or FDA approval as appropriate ?
YES	7. Are there defined ***treatment*** protocols for the condition when identified?
YES	
YES	8. Do the results have ***clinical utility,*** balancing benefits and harms?
	9. Will screening identify those most likely to benefit from treatment?

Nominations and Prioritization Group Recommendations

The Advisory Committee **SHOULD** move the nomination of early onset Metachromatic Leukodystrophy forward for a full evidence review